HORMONE RECEPTOR STATUS IN BREAST CANCER IN RELATION TO HISTOLOGICAL GRADING, AGE AND LYMPH NODE INVOLVEMENT

A DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the regulations for the award of the

Degree of **M.S., (GENERAL SURGERY)**

BRANCH – I

DEPARTMENT OF GENERAL SURGERY

STANLEY MEDICAL COLLEGE AND HOSPITAL

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2014

CERTIFICATE

This is to certify that the dissertation entitled ***"HORMONE RECEPTOR STATUS IN BREAST CANCER IN RELATION TO HISTOLOGICAL GRADING, AGE AND LYMPH NODE INVOLVEMENT"*** is the bonafide work done by ***Dr. R.Rani Suganya,*** Post Graduate student (2011 – 2014) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfillment of the regulations of The Tamil Nadu Dr. M.G.R Medical University, Chennai for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

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DECLARATION

I, Dr. R.Rani Suganya solemnly declare that this dissertation entitled " **HORMONE RECEPTOR STATUS IN BREAST CANCER IN RELATION TO HISTOLOGICAL GRADING, AGE AND LYMPH NODE INVOLVEMENT** " is a bonafide work done by me in the Department of General Surgery, Government. Stanley Medical college Hospital, Chennai under the supervision of my unit chief **Prof. R.V. SURESH. M.S.,** with the guidance of **Prof P.DARWIN. M.S.,** and my Head of the Department **Prof. KAMARAJ.M.S.**

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

Place: Chennai.

Date: December 2013. **DR. R.RANI SUGANYA**

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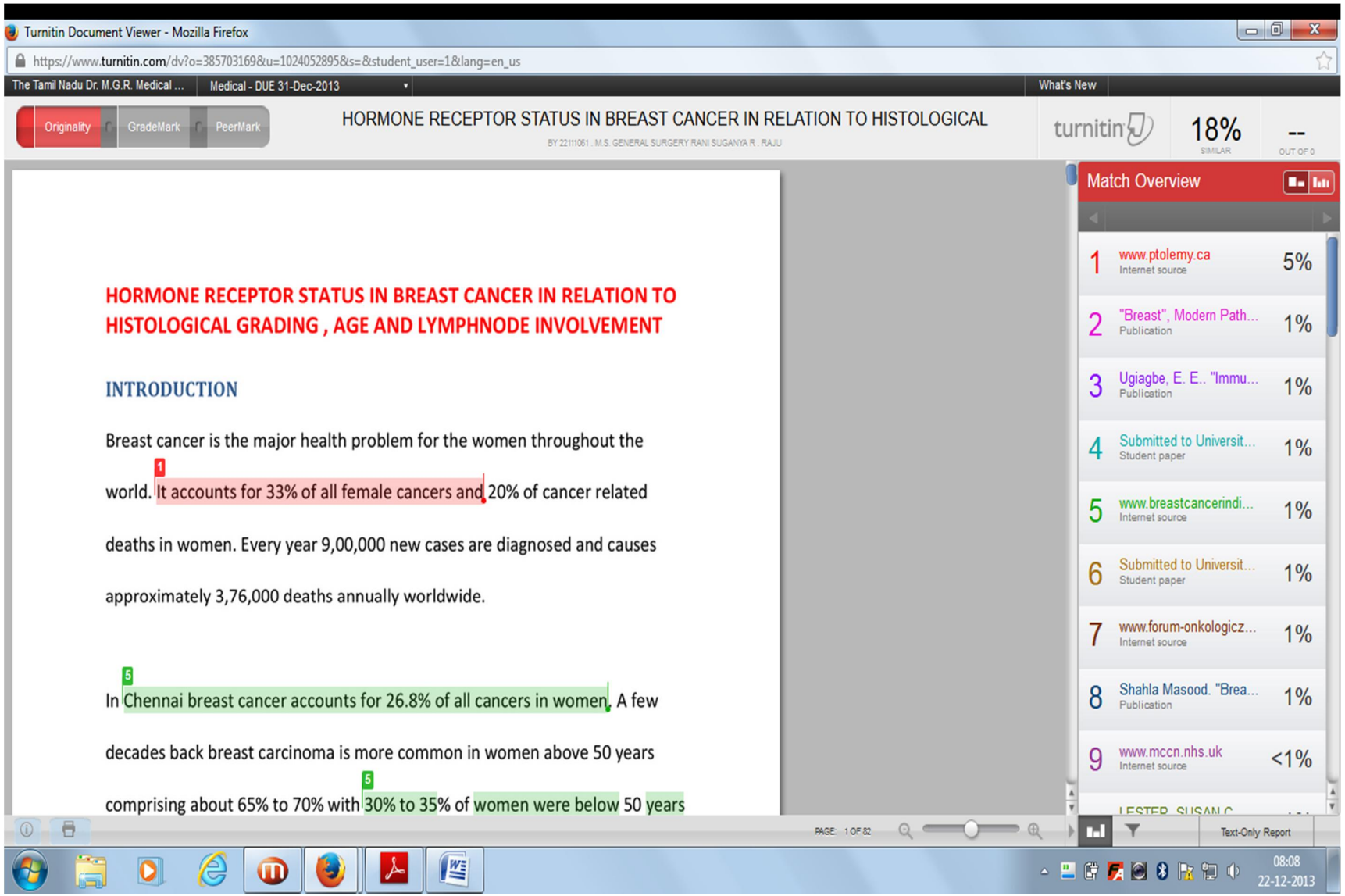
It is my earnest duty to thank my parents without whom accomplishing this task would have been impossible. I am extremely thankful to my patients who consented and participated to make this study possible.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INTRODUCTION
Breast cancer is the major health problem for the women throughout the world. It accounts for 33% of all female cancers and 20% of cancer related deaths in women. Every year 9,00,000 new cases are diagnosed and causes approximately 3,76,000 deaths annually worldwide.
In Chennai breast cancer accounts for 26.8% of all cancers in women. A few decades back breast carcinoma is more common in women above 50 years comprising about 65% to 70% with 30% to 35% of women were below 50 years
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ABSTRACT

TITLE:

Hormone receptor status in Breast cancer in relation to Histological grading, age and lymph node involvement.

AUTHOR:

Dr.Rani Suganya, M.S., General Surgery Post Graduate III Year

KEYWORDS:

Estrogen receptor, Progesterone receptor, HER 2/neu oncoprotein, Grading, Lymphnode , Age.

BACKGROUND:

Aim of the study is to evaluate hormone receptor status and HER 2/neu in breast carcinoma by using immunohistochemical method and to correlate with histological grade, age and lymphnode involvement in breast cancer patients attending General Surgery OPD, Govt. Stanley Medical College Hospital , Chennai.

RESULTS:

From the above study in a group of 50 breast cancer patients, we found that Invasive Ductal Carcinoma-Nos type constituted the most commonest histological variants. Regarding histological grade , Grade II tumours was found to be commonest. Estrogen and progesterone receptor positivity was found in about 70% of cases, whereas HER 2/neu positivity was found in 36% of the tumours. Larger the tumour size lesser is the

expression of hormone receptor status. There is higher receptor expression in nodal negative patienrs.HER 2/neu overexpression is found in about 64% of nodal positive patients. Higher the histological grade lower the receptor positivity and greater the HER 2/neu overexpression. There is an inverse relation between the receptor and HER 2/neu overexpresssion.

CONCLUSION:

Estrogen, Progesterone receptor positive tumours are more common in the post menopausal women, tumours of more than 2cm in size, Histological grade I and in nodal negative patients. Oncoprotein overexpression is common among the tumours of more than 2cm in size, grade III tumours and in nodal positive patients. Hormone receptor and oncoprotein expression has an inverse correlation with each other.

INTRODUCTION

Breast cancer is the major health problem for the women throughout the world. It accounts for 33% of all female cancers and 20% of cancer related deaths in women. Every year 9,00,000 new cases are diagnosed and causes approximately 3,76,000 deaths annually worldwide.

In Chennai breast cancer accounts for 26.8% of all cancers in women. A few decades back breast carcinoma is more common in women above 50 years comprising about 65% to 70% with 30% to 35% of women were below 50 years of age. But at present the scenario has changed with increasing incidence below 50 years of age comprising of about 49%. Breast cancer scenario in India also shows a significant trend of increased incidence of breast cancer in much younger age than earlier.

Management of breast carcinoma has evolved to include both surgery for local disease and medical therapy for systemic disease. Current treatment strategies take into account tumour cells, size and location of the tumour to guide treatment. At present, there are choices of conservative and reconstructive surgery which is more popular than mastectomy due to the availability of increased range of systemic, cytotoxic and hormonal drugs used in neoadjuvant and adjuvant settings.

Prognosis and management of breast carcinoma depends upon the histological type, grade, tumour size, nodal status, hormonal receptor status and HER-2/neu overexpression.

Identification of biomarkers plays an important role in the prognosis and management of breast carcinoma. At the time of diagnosis, determination of hormonal status forms an important step in primary assessment. Identification of Estrogen and Progesterone receptor at the time of diagnosis plays a crucial role to plan for optimal treatment of breast carcinoma.

Estrogen exposure is a well-established predictive and prognostic factor for developing ER-positive breast cancer. Estrogen is a steroid hormone. It has a proliferative effect on normal human mammary epithelium through its activation of Estrogen receptor, a nuclear hormone receptor. ER positivity is overexpressed in as many as 70% of breast cancers. Today, Estrogen receptor remains a very effective target for breast cancer treatment . ER/PR-positive tumours have a better prognosis than ER/PR-negative tumours. Hormone receptor test is done routinely since hormone treatment has fewer side effects and it prevents recurrence in about 25% of cases.

HER2 amplification or protein overexpression is associated with accelerated cell growth and proliferation. It is also associated with an increased risk of recurrence and shortened overall patient survival. The prognosis of HER-2/neu positive tumours are worse than HER2/neu negative tumours. It serves as a marker of aggressive disease and a biologic target for treatment. It is sensitive to treatment with monoclonal antibody Trastuzumab (Herceptin).

Tumour grading is done on the basis of Bloom Richardson grading system. It grades breast carcinoma by adding up scores for tubule formation, nuclear pleomorphism and mitotic count each of which is given a score of 1 to 3.Receptor status together with tumour grade helps to categorize breast cancer into several molecular classes that have different prognosis and may have different responses to specific therapies.

ER, PR and HER 2/neu receptors status are determined using immunohistochemistry method. Response to hormone therapy in ER/PR positive tumours implicate good prognosis. The relationship between ER, PR and HER 2/neu receptor status and tumour grading, lymph node status and age plays an important role in the management of carcinoma breast.

AIMS AND OBJECTIVES OF THE STUDY

1. To evaluate ER, PR receptor status and HER 2/neu oncoprotein expression in carcinoma breast using immunohistochemical method.

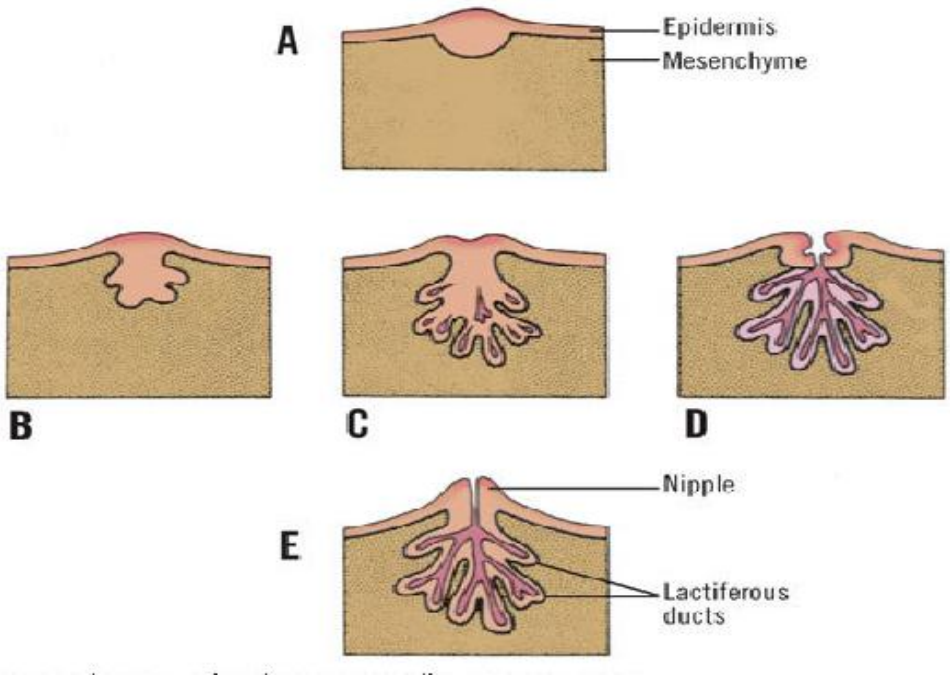
2. To evaluate tumour grading, lymph node status in histopathological specimen

3. To correlate ER, PR and HER 2/neu status with lymph node, tumour grading and age of the patient.

4. To evaluate occurrence of histological variants of carcinoma breast in patients attending OPD in Govt. Stanley Medical college Hospital.

REVIEW OF LITERATURE

EMBRYOLOGY OF THE BREAST`



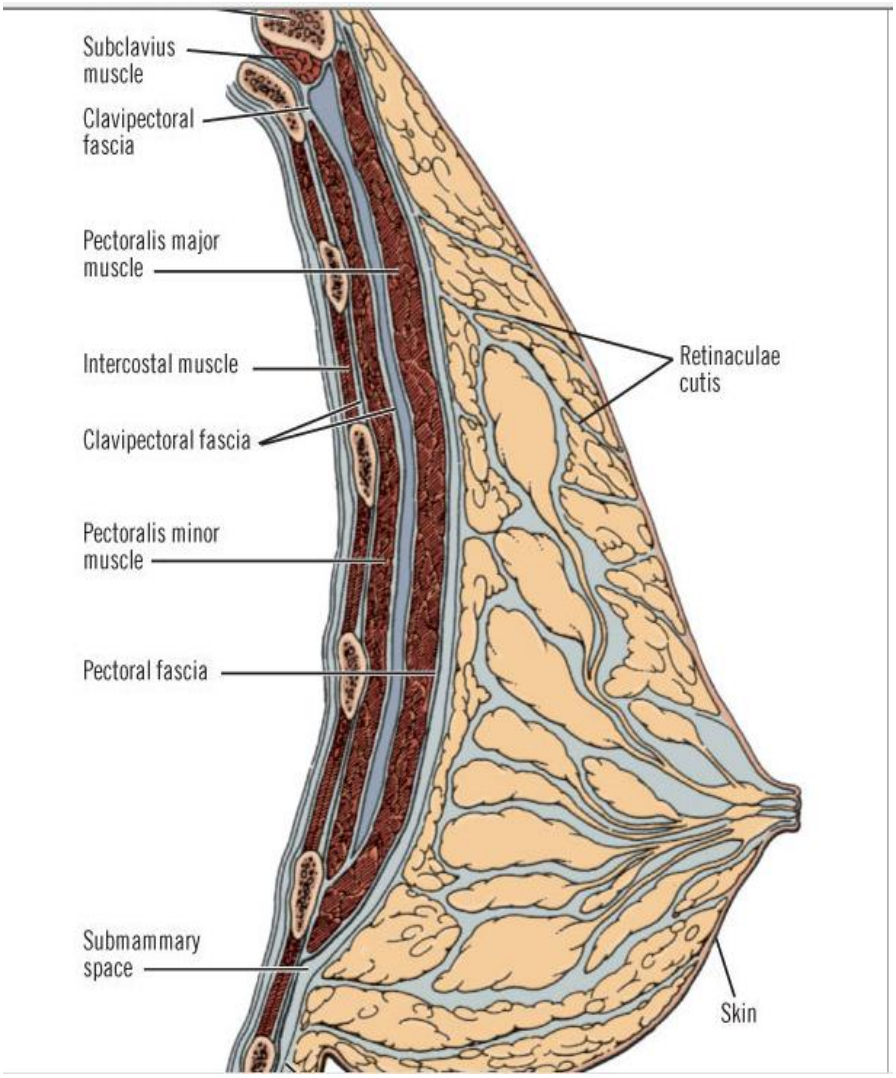
A. TO D : Stages In The Formation Of Duct System And Potential Glandular Tissue From The Epidermis.

E : Eversion of the Nipple Near Birth.

At about fifth or sixth week of fetal life, two ventral bands of thickened ectoderm develop called as milk line or mammary ridge extending from foregut to hindlimb. These may disappear after a short time except for a small portion which may persist in the pectoral region.

Ingrowth of ectoderm in each breast forms the primary bud. This primary bud inturn forms 15 to 20 secondary buds. Epithelial cords develops from the secondary bud and extends into the surrounding mesenchyme forming lactiferous ducts. These lactiferous ducts opens into the shallow mammary pits. In infancy proliferation of mesenchyme transforms the mammary pit into a nipple. At birth, breasts of both males and females are identical.

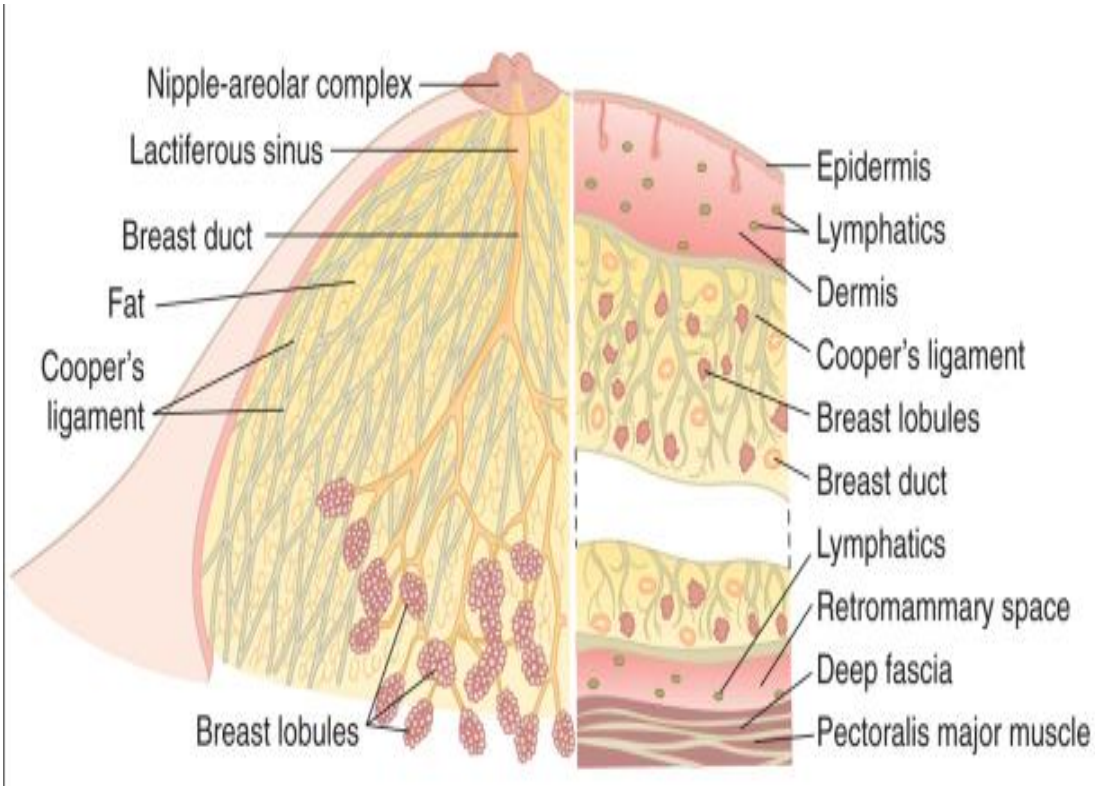
FUNCTIONAL ANATOMY



The female breast extends from the level of second or third rib superiorly to the level of sixth or seventh rib inferiorly. It extends transversely from the lateral border of sternum medially to the anterior axillary line laterally. The posterior surface of the breast lies on the fascia of the pectoralis major, serratus anterior and external oblique muscles and the upper extent of the rectus sheath. The retromammary bursa is present in between the investing fascia of the breast and the fascia of the pectoralis major muscles. The portion of the breast that lie across the anterior axillary fold is called the axillary tail of Spence

The breast is composed of 15 to 20 lobes. Each lobes are composed of several lobules. Suspensory ligament of Cooper are fibrous connective tissue that pass through the breast tissue to the dermis to provide structural support to the breast. Large volume of breast tissue are found in the upper outer quadrant than in any other quadrants.

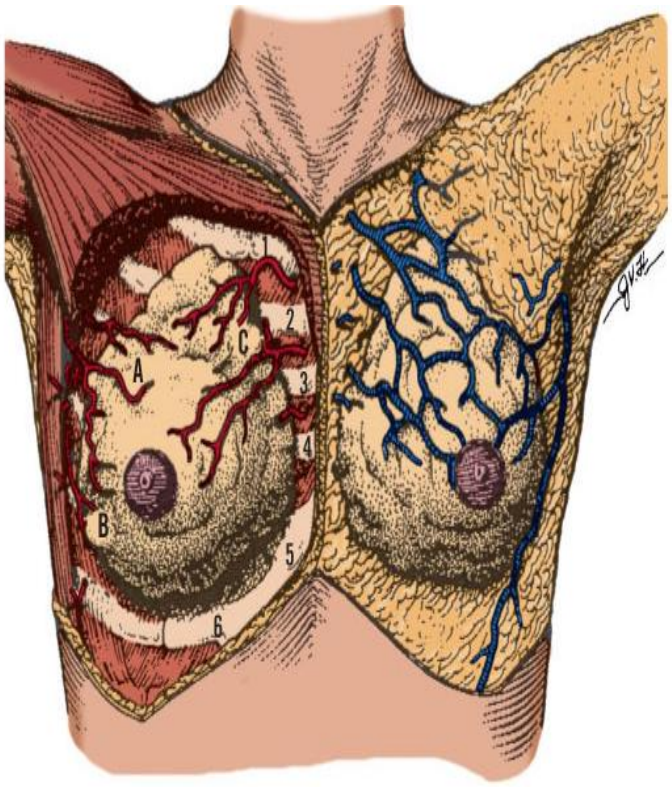
NIPPLE AND AREOLA



The nipple and areola complex is pigmented and corrugated. During puberty, the pigment over the nipple becomes darker and assumes an elevated configuration. During pregnancy, there is deepening of the pigmentation and the areola enlarges. Sweat glands, sebaceous glands and accessory glands are present in the areola and it produces small elevations on the surface of the areola and they are called as Montgomery tubercles. There are smooth muscle fibres that lie circumferentially in the dense connective tissue and longitudinally along the major ducts and extend in to the nipple. They are responsible for the nipple erection that occurs with various sensory stimuli. Moreover the tip of the nipple contains numerous sensory nerve endings and Meissner's corpuscles. This

sensory innervation is responsible for the initiation of chain of neurohumoral events when the infant sucks that results in milk letdown.

BLOOD SUPPLY



A - Direct mammary branches of the axillary artery.

B - Branches of lateral thoracic artery.

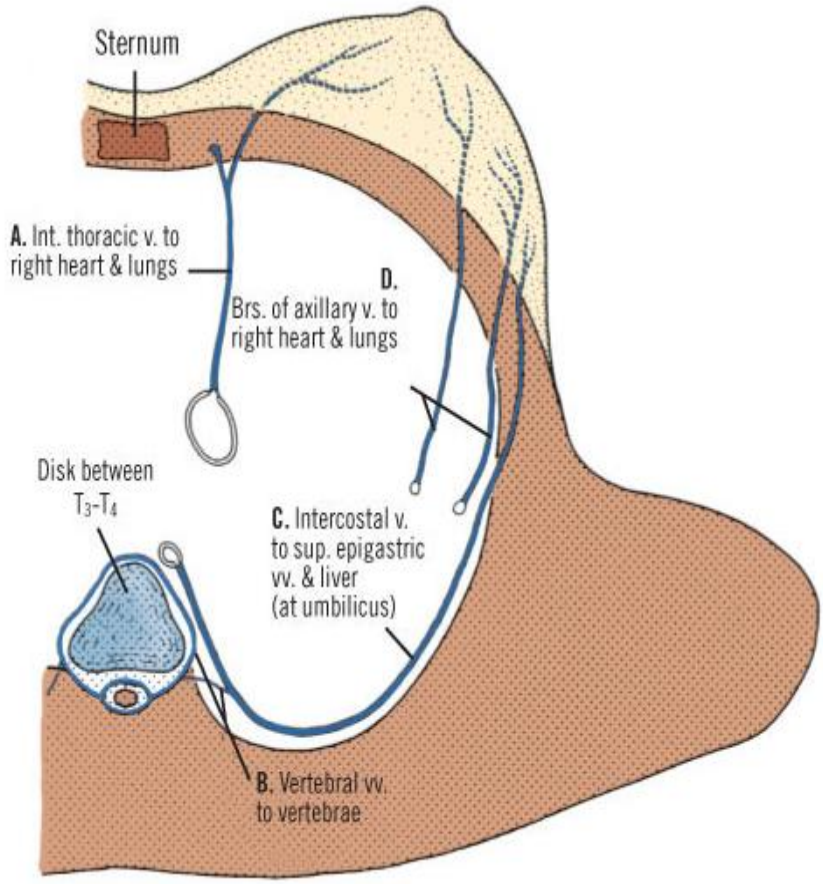
C - Perforating branches of internal thoracic artery.

The principle blood supply are from

1. Perforating branches of the internal mammary artery.
2. Lateral branches of the posterior intercostals arteries.

3. Branches from the axillary artey including lateral thoracic artery and pectoral branch of thoracoacromial artery.
4. Medial mammary artery is formed by the arborising branches of the internal mammary artery and second, third and fourth anterior intercostal perforators.
5. The pectoralis major, pectoralis minor, serratus anterior and subscapularis muscle receive branches from the lateral thoracic artery.

VENOUS DRAINAGE

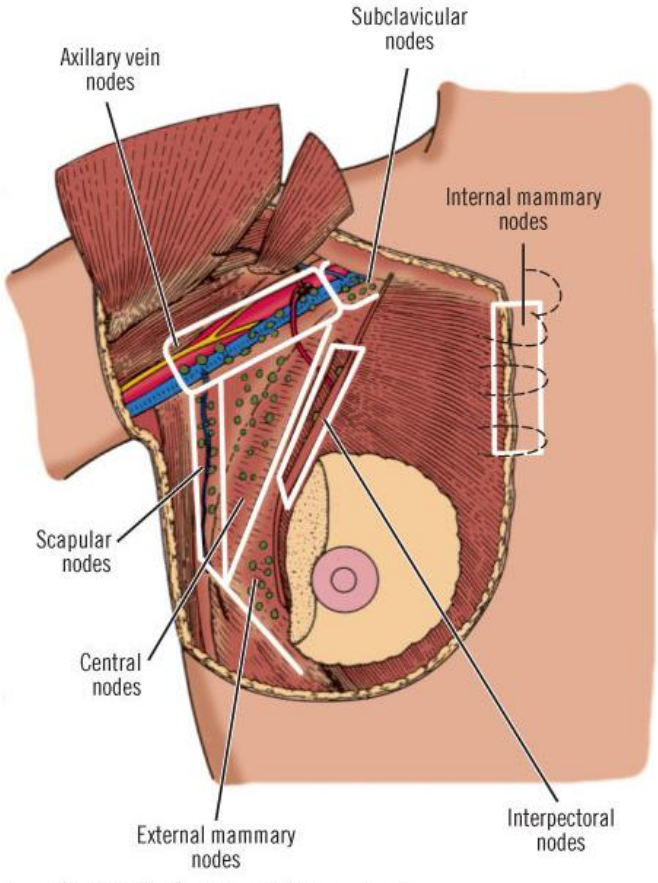


The principle group of veins are

1. Perforating branches of the internal thoracic vein.
2. Perforating branches of the posterior intercostal veins.
3. Tributaries of the axillary vein.
4. Vertebral plexus of Batson invests the vertebra and extends from the base of the skull to the sacrum is responsible for the breast cancer metastases to the vertebrae, skull, pelvic bones and the brain.

LYMPHATIC DRAINAGE

The principle group of axillary lymph nodes are



1. Axillary group or lateral group consists of 4 to 6 lymph nodes which lie on the medial or posterior aspect of the vein and receives lymphatic drainage from the upper extremity.

2. External mammary or anterior or pectoral group consists of 5 to 6 lymph nodes and lie along the lower border of pectoralis minor muscle and receive lymphatic drainage from the lateral aspect of the breast.

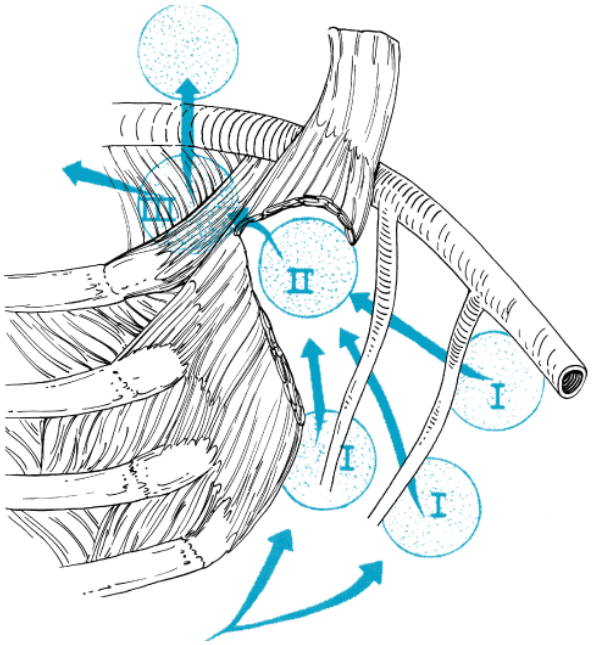
3. The scapular or subscapular or posterior group consists of 5 to 7 lymph nodes lies along the lateral border of the scapula and receives lymphatic from the lower posterior neck, posterior shoulder and posterior trunk.

4. The central group consists of 3 to 4 lymph nodes and lie along the posterior border of the pectoralis minor muscle and receives lymphatics from the axillary, external mammary and the scapular group and also directly from the breast.

5. The subclavicular group consists of 6 to 12 lymph nodes and lie along the superior and upper border of pectoralis minor muscle and receives lymphatics from the other axillary groups.

6. The interpectoral group or Rotter’s nodes consists of 1 to 4 lymph nodes lies between the pectoralis major and minor muscle and receive lymphatics from the breast.

The lymph nodes are grouped into levels in relation to the pectoralis minor



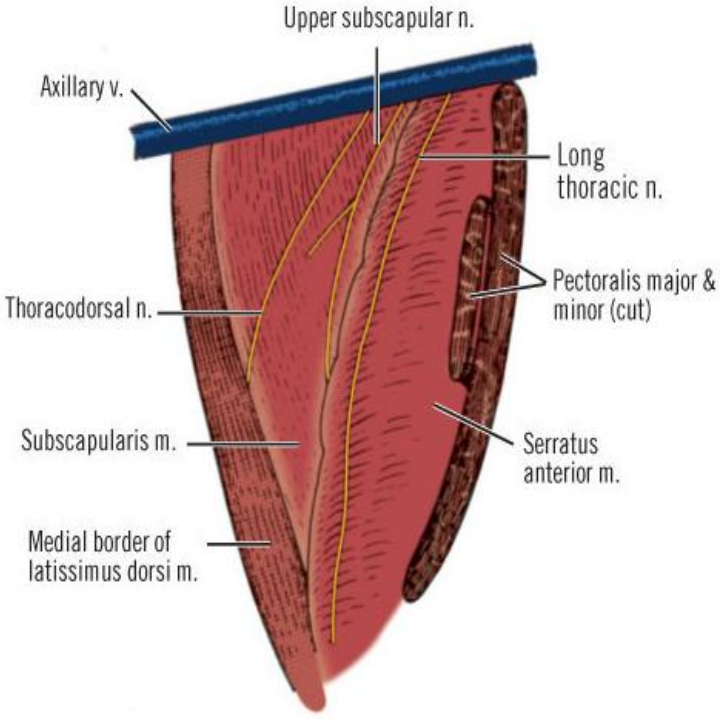
1. Level I lymph nodes are located lateral to the lower border of pectoralis minor muscle and includes axillary, external mammary and scapular groups.

2. Level II lymph nodes are located posterior to pectoralis minor muscle and includes central and interpectoral groups.

3. Level III lymph nodes are located superior to medial border of pectoralis minor muscle and includes subclavicular group.

The lymphatic plexus of the breast arises in the interlobular connective tissue and major lactiferous duct and traverses to the subareolar plexus of Sappey. Efferents from the breast travel along the lateral border of the pectoralis major muscle and pierces the clavipectoral fascia to reach the external mammary group. Some reach the axillary and the scapular group. 75% of the lymphatics from the breast reach the axillary lymph nodes. Rest of the lymphatics reach the internal mammary lymph nodes, primarily from the medial aspect of the breast.

NERVE SUPPLY

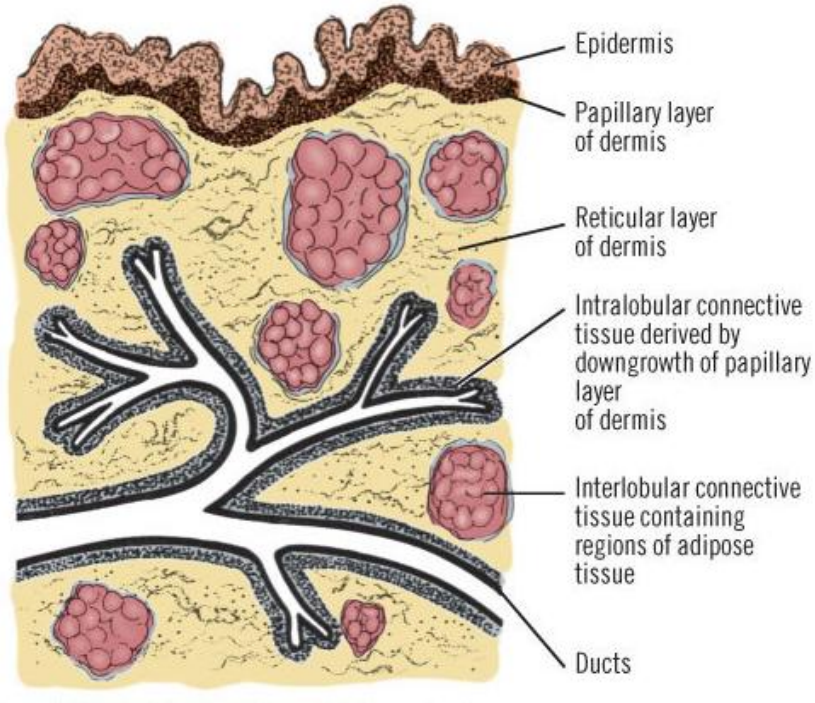


1. Lateral cutaneous branches of the third to sixth intercostals nerves provide sensory supply to the breast and the anterolateral chest wall.

2. Cutaneous branches of the cervical plexus specifically the anterior branches of the supraclavicular nerves supply a limited area of the skin of the breast.

3. Intercostobrachial nerve, lateral cutaneous branch of the second intercostals nerve supplies the medial aspect of the upper arm, which is often encountered in axillary dissection.

MICROSCOPIC ANATOMY



The mature breasts composed of

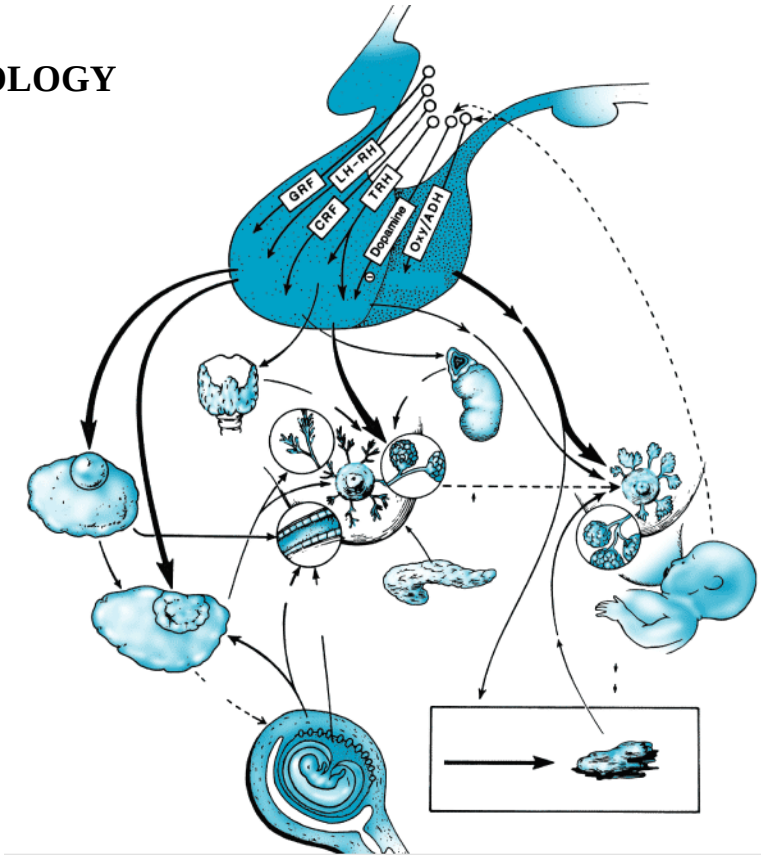
1. Glandular epithelium
2. Fibrous stroma and supporting structures
3. Fat and infiltrating cells including lymphocytes and macrophages.

The glandular apparatus of the breast is consists of branching system of lactiferous ducts extending outwards and downwards from the nipple areolar complex. These ducts ends in cluster of spaces called as terminal ductules or acini. The terminal ductules together with small

efferent ductules form the lobules. These are the milk forming glands. The lactiferous ducts in the subareolar region widens to form the lactiferous sinuses which opens through 10 to 15 orifices in the nipple. These ducts are lined by low columnar or cuboidal epithelium.

The branching ductal system is surrounded by myoepithelial cells which have contractile properties that propel the milk formed in the lobules towards the nipple. The basement membrane surrounds the epithelial and myoepithelial cells of the ducts and is made up of laminin, type IV collagen and proteoglycans. The basement membrane is important in differentiating between carcinoma in situ and invasive cancer.

PHYSIOLOGY



Hormones like estrogen, progesterone, prolactin, thyroid hormone, oxytocin, cortisol and growth hormone are essential for the normal development and function of the breast. Development of ductal epithelium is initiated by estrogen and differentiation of the ductal epithelium and the lobular development by the progesterone hormone. The hormonal stimulus for lactogenesis is prolactin.The release of estrogen and progesterone from the ovaries are stimulated by gonadotropic hormones like luteinizing hormone (LH) and follicle stimulating hormone (FSH). Basophilic cells of anterior pituitary secrete LH and FSH, which is regulated by the release of gonadotropin releasing hormone (GnRH) from the hypothalamus, which in turn is controlled by the positive and negative feedback effects of the circulating estrogen and progesterone.

After birth, circulating estrogen and progesterone levels fall and remain low till puberty, due to the effect of negative feedback on the hypothalamic pituitary axis. At puberty, there is decrease in the sensitivity of the negative feedback on the hypothalamic pituitary axis and increase sensitivity to positive feedback by estrogen hormones. These in turn stimulate the secretion of GnRH, FSH, LH and ultimately the secretion of estrogen and progesterone, estabilishing the menstrual cycle.

During prepuberty the breast is composed of fibrous stroma and few ducts lined with epithelium. With the onset of menstrual cycle, there is commencement of breast engorgement and duct epithelium proliferation. Breast development are initiated by low amplitude of pituitary gonadotrophins, which increase estradiol level. This causes increase in deposition of fat, branching system of ducts and lobular units.

During pregnancy, the circulating ovarian and placental estrogen and progesterone causes the breast to enlarge with the proliferation of ductal and lobular epithelium. The accessory glands of Montgomery becomes prominent and the areolar skin darkens. The minor ducts develop and branch during the first and second trimester. During the third trimester colostrums fills the ductal spaces and alveolar epithelium.

After delivery, the circulating progesterone and estrogen levels fall, with increase in the level of prolactin which stimulates milk production and secretion. This is controlled by the neural reflex arc from the nerve endings of the nipple-areola complex. With menopause the estrogen and progesterone levels decrease causing involution of the ducts and alveoli, increase in the density of the fibrous tissue and fat.

INCIDENCE AND EPIDEMOLOGY

Breast cancer is the major health problem for the women throughout the world. It accounts for 33% of all female cancers and 20% of cancer related deaths in women. Every year 9,00,000 new cases are diagnosed and causes approximately 3,76,000 deaths annually worldwide.

In Chennai breast cancer accounts for 26.8% of all cancers in women. A few decades back breast carcinoma is more common in women above 50 years comprising about 65% to 70% with 30% to 35% of women were below 50 years of age. But at present the scenario has changed with increasing incidence below 50 years of age comprising of about 49%. Breast cancer scenario in India also shows a significant trend of increased incidence of breast cancer in much younger age than earlier.

There is a sharp increase in the incidence of breast carcinoma due to the increased awareness and widespread use of screening mammography. However, mortality from breast carcinoma decreases due to early detection and multimodality treatment.

RISK FACTORS

Multiple factors are associated with the increased risk of developing breast cancer.

FAMILIAL FACTORS

True hereditary predisposition exists in about 5% to 10% of the cases. The risk of developing breast cancer is 1.5 to threefold if the woman has first degree relative with breast cancer.

GENETIC FACTORS

Mutations in BRCA 1 and BRCA 2 gene is associated with increased risk of developing breast and ovarian carcinoma. It accounts for 5% to 10% of breast carcinoma. It is inherited in autosomal dominant fashion.

The histological features in BRCA 1 mutation has high incidence of medullary features and grade 3 tumours. In BRCA 2 mutations it is predominantly tubular and lobular variants.

HORMONAL FACTORS

1. Increased exposure to endogenous estrogen – Early age at menarche, late menopause, nulliparity, delayed age at full term pregnancy increase the risk of breast carcinoma.

2. Obesity and postmenopausal hormone replacement therapy increases the risk of breast carcinoma.

DIETARY AND LIFESTYLE FACTORS

1. Diet high in fat is associated with increased risk of breast carcinoma.

2. Risk increases linearly with increased alcohol consumption.

3. Decreased intake of vitamin c, beta carotene and folate is associated with increased risk.

BENIGN BREAST DISEASE

Proliferative breast disease with features of atypical hyperplasia is associated with increased risk of breast carcinoma.

ENVIRONMENTAL FACTORS

Exposure to ionising radiation, electromagnetic fields, organochlorine pesticides at younger age before the age of 15 is associated with increased risk of breast carcinoma.

ETIOLOGY AND PATHOGENESIS

Breast carcinoma can be divided based on the risk factor into

1. Sporadic breast carcinoma.

2. Hereditary breast carcinoma.

HEREDITARY BREAST CARCINOMA

25% of familial cancers are due to mutation in the genes BRCA 1 and BRCA 2, located in the chromosomes 17q21 and 13q12.3 respectively. Both of them are tumour suppressor genes. Mutation in these genes results in uncontrolled proliferation of the breast epithelium resulting in breast carcinoma. BRCA 1 carcinoma has predominant histopathological characteristic of medullary carcinoma. BRCA 2 tumours does not have distinct morphological characteristic.

SPORADIC BREAST CARCINOMA

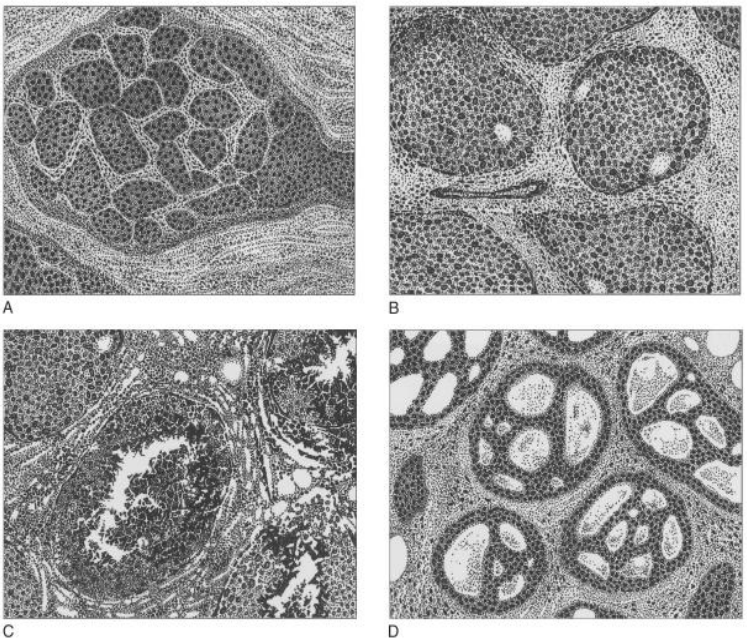
Sporadic breast carcinoma is associated with major risk factors related to early menarche, late menopause, duration of exposure to estrogens, exogenous exposure to estrogens. These carcinomas overexpress estrogen receptors.

CLASSIFICATION OF PRIMARY BREAST CANCER

NONINVASIVE EPITHELIAL CANCER

1. Lobular carcinoma insitu (LCIS)

2. Ductal carcinoma insitu or intraductal carcinoma.(DCIS) Papillary, cribriform, solid and comedeo types.



A- LCIS

B- DCIS solid type

C- DCIS comedo type

D- DCIS cribriform type

INVASIVE EPITHELIAL CANCER

Invasive lobular carcinoma

Invasive ductal carcinoma

Invasive ductal carcinoma, NOS

Tubular carcinoma

Mucinous or colloid carcinoma

Medullary carcinoma

Invasive cribriform carcinoma

Invasive papillary carcinoma

Adenoid cystic carcinoma

Metaplastic carcinoma

MIXED CONNECTIVE AND EPITHELIAL TUMOURS

Phylloides tumours, benign and malignant

Carcinosarcoma

Angiosarcoma

NOS, not otherwise specified.

MICROSCOPIC TYPES OF BREAST CARCINOMA

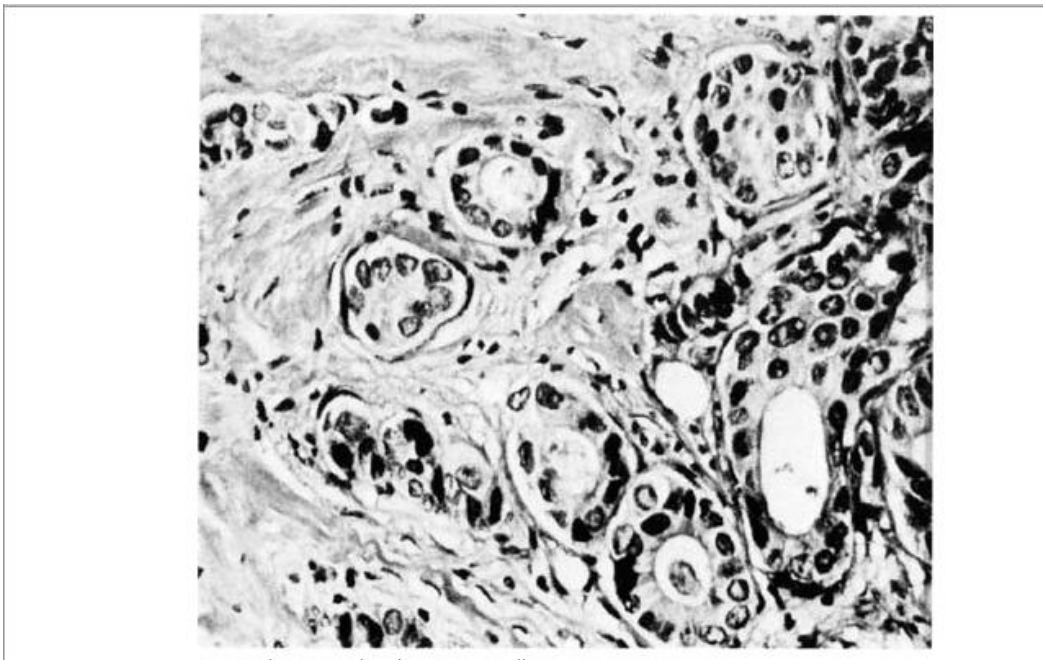
NONINVASIVE BREAST CANCER

Noninvasive breast cancers are lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS).Lobular carcinoma in situ is considered as risk factor for breast cancer and is characterised by normal outline of the lobule , with expanded filled acini. Ductal carcinoma in situ is a heterogenous lesion with four types namely papillary, solid, cribriform and comedo. DCIS is characterised by discrete spaces with normal basement membrane filled with malignant cells surrounded by normal epithelial cells. Papillary and cribriform types are of lower grade. The solid and comedo types are high grade lesions. The malignant cells within the ductal membrane proliferate and undergoes central necrosis, because blood supply to these cells are outside the basement membrane. These necrotic debris undergoes calcification and can be detected in mammogram as segmental calcification. DCIS coexists with invasive cancers.

INVASIVE BREAST CARCINOMA

Tumours that are included in this group are those that exhibit stromal invasion. This include lobular carcinoma and ductal carcinoma.

INVASIVE DUCTAL CARCINOMA – NOS TYPE

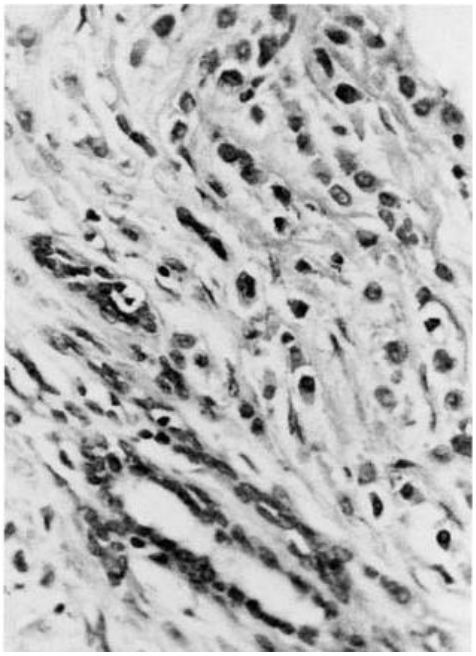


It accounts for 80% of breast cancers. It presents with microscopic or macroscopic lymph node metastases. Most common in perimenopausal and postmenopausal women. According to WHO classification, invasive ductal carcinoma is most frequent and it should not fall into other types of invasive breast carcinoma.

Microscopically to diagnose invasive ductal carcinoma NOS type, there should be a non specialised pattern in over 50% of tumour area. A pattern of trabecular, infiltrative margins, acinar, diffuse sheet like and nested patterns are noted. Hitologically they are graded into well differentiated, moderately differentiated and poorly differentiated based on pleomorphism, tubule formation and mitotic count.

Hormone receptor studies of invasive ductal carcinoma NOS type shows 80% of ER/PR positivity and 30% of HER 2 neu positivity.

INVASIVE LOBULAR CARCINOMA (ILC)



The term infiltrating lobular carcinoma was introduced by Foot and Stewart. It accounts for 10% of breast carcinomas. Microscopically it is composed of small cells with round nuclei, small amount of cytoplasm and inconspicuous nucleoli. Intracytoplasmic mucin displace the nucleus peripherally , signet-ring cell carcinoma. It is multicentric , multifocal and often bilateral.

Receptor assay reveals ER/PR positivity in 62% to 90%, E-Cadherin negativity and HER 2 neu negativity.

MUCINOUS CARCINOMA

Mucinous carcinoma also called as colloid carcinoma , accounts for about 2% of all invasive beast carcinoma. More common in elderly females. Presents as bulky tumour. Microscopically, it is characterised by the presence of extracellular pools of mucin surrounded by aggregates of low grade malignant cells. The cut surface of the tumour shows glistening and gelatinous surface, with areas of fibrosis. The degree of fibrosis imparts a firm consistency to the tumour. About 66% of mucinous carcinomas exhibit hormone receptors. 33% of cases exhibit lymph node metastases. Survival rates at 5 and 10 years are 73% and 59% respectively. Mucinous carcinoma shows HER 2/neu negativity.

MEDULLARY CARCINOMA

Medullary carcinoma is a high grade tumour. The tumour is a well circumscribed mass and it is soft in consistency. According to WHO medullary carcinoma is defined as a well circumscribed carcinoma composed of poorly differentiated cells with prominent lymphocytic infiltration and scant stroma. Inspite of high grade, it has a relatively good prognosis.

IHC studies shows negativity to estrogen expression and they exhibit immunophenotype p53 positive and HER-2/neu negative.

NEUROENDOCRINE CARCINOMA

Nuroendocrine carcinoma was first described by Coombes RC in the year 1975. In the year 1977 Cubilla AL at al described in eight patients a new entity called primary carcinoid tumour. WHO defines neuroendocrine carcinoma when the tumour exhibits neuroendocrine marker positivity in more than 50% of the tumour cell population. It accounts for 10% to 18% of all invasive breast carcinoma.

Microscopically it has infiltrative pattern composed of cells arranged in sheets, nests or trabecular formation with peripheral pallisading of cells.

IHC shows 67% of the tumour exhibits estrogen positivity and 56% of the tumour exhibits progesterone positivity. HER-2/neu overexpression is negative in this type of carcinoma.

PAPPILARY CARCINOMA

It is a rare carcinoma in which invasive histopathological feature with predominant papillary structure is characteristic.

IHC shows Estrogen receptor and progesterone receptor positivity and HER-2/neu negativity.

CARCINOMA WITH METAPLASIA

WHO publication in the year 2003 defined metaplastic carcinoma as heterogenous neoplasm composed of spindle cells, mesenchymal cells with mesenchymal differentiation.

IHC studies shows hormone receptors and HER-2/neu negativity and they are positive for keratin, EMA and S100.

TUBULAR CARCINOMA

It accounts for about 2% of the invasive breast carcinoma. It is more common in the perimenopausal and early menopausal age. Microscopically the cellular pattern are arranged in tubular pattern. 10% of the cases develop lymph node metastases and usually to the level I axillary group of lymph nodes. However the presence of distant metastases does not affect the survival.

PROGNOSTIC AND PREDICTIVE FACTORS FOR INVASIVE CARCINOMA

Prognostic and predictive factors are grouped into tumour factors and host factors.

Tumour factors include nodal status, tumour status, histologic grade, lymphovascular invasion, pathologic stage, hormone receptor status, DNA content, extensive intraductal component.

Host factors include age, menopausal status, family history, previous breast cancer, immunosupression, nutrition, prior chemotherapy, prior radiation therapy.

1. LYMPH NODE STATUS

In invasive breast carcinoma axillary lymph node status is the most important prognostic factor. Macrometastases greater than 0.2 cm has an important prognostic significance.

2. TUMOUR SIZE

Tumour size which is an important component of TNM staging is an another important prognostic factor. It is independent of nodal status.

3. HISTOLOGIC GRADE

The degree of tumour differentiation in invasive breast carcinoma is assessed using Bloom Richardson grading system. It includes tubule formation, nuclear grade and mitotic rate. Each element is given a score of 1 to 3 with 1 for best prognosis and 3 for the worst prognosis.

Tubule formation

More than 75% of the tumour 1

10% to 75% of the tumour 2

<10% of the tumour 3

Mitotic count

0 to 9 mitoses/10 hpf 1

10 to 19 mitoses/10 hpf 2

20 or > mitoses/10 hpf 3

Nuclear Pleomorphism

Small regular uniform cells 1

Moderate nuclear size 2

Variation

Marked nuclear size variation 3

COMBINED HISTOLOGIC GRADE

Low Grade I	3-5
Intermediate Grade II	6-7
High Grade III	8-9

4. LYMPHOVASCULAR INVASION

Tumour cells may present within the lymphatics or within the capillaries surrounding the tumour. Presence of lymphovascular invasion is the strong predictor of survival outcome and is a poor prognostic indicator.

5. PATHOLOGICAL STAGE

The survival rate of women with special types of invasive carcinoma like mucinous, tubular, medullary, lobular and papillary is 60% when compared with women with cancers of no special type which is less than 20%.

6. ESTROGEN AND PROGESTERONE RECEPTORS

Immunohistochemistry assays are used to study the hormone receptor status. Women with hormone receptor positive have better prognosis than hormone receptor negative.

7. HER-2/neu

HER-2/neu or human epidermal growth factor receptor 2 is a transmembrane glycoprotein. It's main function is control of cell growth. Overexpression of HER-2/neu is a bad prognostic factor.

8. DNA CONTENT

Those tumours with aneuploidy have abnormal DNA indices and are associated with bad prognosis. The amount of DNA present in each individual cell can be assessed by flow cytometric analysis. It can also be done by image analysis of tissue sections.

9. MICROMETASTASIS

In node negative breast cancer microscopic foci of tumour metastasis can be found in 9% to 13% of cases. The prognosis of patients with micrometastasis is (defined as less than 2 mm in diameter) same as that of in patients with node negative status.

10. TUMOUR ANGIOGENESIS

Growth of new blood vessels adjacent to the tumour determines the risk of metastasis. More the number of blood vessels, more the risk of distant metastasis.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry over the past two decades has evoloved into a revolutionary diagnostic tool in the practice of pathology. The identification of highly specific epitopes in paraffin wax embedded tissues with an antibody and labelling system is the procedure usually followed in cellular pathology. Immunohistochemistry is useful in a number of cases where morphology and clinical data alone are not sufficient for a firm diagnosis of the type of disease in tissue section.

It was Francois VincentRaspard, botanist to first use immunohistochemistry. Immunohistochemistry revolutionized by the advent of aniline dyes during the year 1862 to 1929. The technique we use today owe much to the diligent work done by some key researchers over the past sixty decades. In the year 1941, paper by Coons et al. has significant influences on the development of the fluorescent labelled antibody technique.

Later in the year 1966 the indirect technique was introduced by Nakane and Pierce, in that unlabelled antibody is followed by a second substrate or antibody. Immunohistochemistry developed through stages from peroxidase-antiperoxidase (1970), Labelling with Alkaline Phosphatase (1971), Avidin – biotin technique (1977, 1979) and to double layer dextrin polymer technique (1993) which carries both disadvantages and advantages for each techniques.

DEFINITIONS

IMMUNOHISTOCHEMISTRY

It is a technique for identifying tissue or cellular constituents (antigen) by means of antigen – antibody interactions. The antibody site being identified either by use of a secondary labelling method or by direct labelling of the antibody.

ANTIGENS

An antigenic carbohydrate, protein or lipid molecule has one or more antibody binding sites. These regions composed of a small number of monosaccharide or aminoacid units and are known as antigenic determinant groups or epitopes.

ANTIBODIES

Antibodies are a class of serum proteins and they are called as immunoglobulins. They are formed in the humoral immune system after recognition of a foreign antigen by plasma cells, the end cell of B cell transformation. IgA, IgD, IgE, IgG and IgM are the five types of antibodies found in the blood. IgG is the most commonest antibody and is the most commonly used antibody in immunohistochemistry.

DETECTION SYSTEM

Two methods are employed for the detection of antigen – antibody reaction complex

1. Direct method.
2. Indirect method.

DIRECT METHOD

In this technique the primary antibody is conjugated directly to the label. Those which are labelled directly with a fluorochrome are the most popularly used direct conjugates. Horse radish peroxidase and alkaline phosphatase directly labelled antibodies are occasionally used.

ADVANTAGE

1. Simple to use.

2. Require one application of regeant, followed by application of the appropriate chromogen substrate.

DISADVANTAGE

1. Sensitivity is low

2. Unable to detect small amounts of antigen that is essential for the diagnosis.

INDIRECT METHOD

This technique involves application of unconjugated primary antibody followed by the application of a labelled antibody. Horse radish peroxidase is the most commonly used label. It is a more sensitive technique, rapid and relatively less expensive.

CURRENT TECHNIQUES

A novel technique reported by Pluzek et al. in 1993 is an Enchanced polymer one step staining method (EPOS) which is a new direct technique. In this technique a large number of primary antibody

molecules along with peroxidase enzymes are attached to a dextran polymer “backbone”. This method is rapid, especially for frozen sections, able to detect small amount of antigen present in the tissue and reproducibility present.

A new indirect technique called as Dextran polymer conjugate Two – Step visualisation technique described by Dako A/S, is based on the dextran technology used in the EPOS system. It is less time consuming.

ANTIGEN RETRIVAL IN IMMUNOHISTOCHEMISTRY

The following technique can unmask antigen in routinely processed tissues.

1. Proteolytic enzyme digestion
2. Microwave antigen retrival.
3. Pressure cooker antigen retrival
4. Microwave and trypsin antigen retrival.

PROTEOLYTIC ENZYME DIGESTION

Huang et al. (1976), Curran & Gregory (1977) and Mepham et al. (1976) described a technique of pre-treating formalin fixed paraffin sections with proteolytic enzymes to unmask the antigenic determinants. The most popular enzymes used are protease and trypsin. It is used for demonstrating immunoglobulins and complement in renal biopsies. It pitfalls include over digestion, antigen destruction and under digestion.

MICROWAVE ANTIGEN RETRIVAL

It involves boiling of dewaxed formalin fixed paraffin sections with a number of solutions and allows rapid and uniform heating. Proliferation markers such as anti-Ki67 and MIB1, which was previously used only on frozen sections, now can be used after heat pre-treatment on paraffin wax sections.

PRESSURE COOKER ANTIGEN RETRIVAL

Replacing the microwave oven with the pressure have showed to have some advantages by Norton et al. (1994). Microwave allows limited numbers, constant attention, time consuming and microwaving of large number of slides result in inconsistencies. But in pressure cooking

methods no such inconsistencies are encountered and is less time consuming.

MICROWAVE AND TRYPSIN ANTIGEN RETRIVAL

Sandison et al. (1994) reported that a combination of microwave antigen retrival followed by trypsin digestion enables more reliable identification. Pitfalls include pre-treatment of the tissues by microwaving makes the tissue very sensitive to proteolytic enzyme digestion.

USES OF IMMUNOHISTOCHEMISTRY IN BREAST PATHOLOGY

1. Evaluation of estrogen and progesterone receptor status by using specific antibodies to the estrogen and progesterone receptor proteins.

2. Evaluation of HER-2/neu protein overexpression by using specific antibodies to the HER-2/neu receptor protein.

3. Differentiating in situ carcinoma from invasive carcinoma by using antibodies to basement membrane proteins (type IV collagen, laminin) and to myoepithelial markers such as actins, calponin, smooth muscle myosin heavy chain.

4. Evaluation of metastatic lesions of possible origin from the breast by using antibodies to ER, GCDFP, CK 7/CK 20 and other markers.

5. Assessment of spindle cell lesions (mesenchymal lesions vs metaplastic carcinoma).

6. Differentiating lobular in situ carcinoma from ductal carcinoma in situ by using antibodies to E-cadherin.

HORMONE RECEPTORS

Elwood V.Jensen was the first person to identify the estrogen receptors in the year 1958, at the University of Chicago. Later in the year 1996, the gene for the second estrogen receptor (ERß) was identified by Kupier et al. ER/PR receptors are nuclear receptors and are in about 7% of epithelial cells of the normal breast tissue. They are more abundant in the lobular cells than the ductal cells.

Two classes of estrogen receptors exists namely ER, is an intracellular receptor and GPER, a G protein coupled receptors. They are stimulated by the hormone 17β estradiol. Alpha and Beta are two different isoforms of estrogen receptors. Alpha receptor encoded by 6p25.1 is found in breast cancer cells, endometrium and in ovarian

stromal cells and in males in efferent ducts. Beta receptor encoded by 14q is found in ovarian granulosa cells, kidney, brain, bone, heart, lungs, prostate and endothelial cells. Progesterone receptor is regulated by the estrogen receptor, thereby it is an indicator for intact ER functional pathway.

Without stimulation the estrogen receptors are located in the cytosol. Only upon stimulation by the estrogen hormone the receptor migrate from the cytosol into the nucleus. Dimerization of the receptor complex occurs and bind to the DNA. This DNA- receptor complex causes transcription of DNA to mRNA and activates MAPK/P13K pathway and causes change in cell function. Moreover estrogen is a steroid hormone and does not require a membrane bound receptors for them to bind with the estrogen receptor.

Two hypotheses have been proposed for its tumourogenesis. One hypotheses states that the transcription activity is induced by the estrogen receptor by alternative RNA splicing of estrogen receptor alpha subunit thereby causing accumulation of genetic mutation and rapid uncontrolled proliferation. The other hypotheses states that tumourogenesis is due to accumulation of the toxic genomic wastes.

Hormone receptors helps in predicting the response to endocrine therapy and they are well established markers for carcinoma breast. Receptors can be assessed on either frozen section or on paraffin blocks by immunohistochemistry. Immunohistochemistry is found superior to Ligand Binding Assay (LBA).

PROGESTERONE RECEPTOR

It is an intracellular steroid receptor that binds to the hormone progesterone. It is controlled by the estrogen receptor and is encoded by the gene PGR 11q22. It is dependent in the estrogen functional pathway. Progesterone hormone stimulates the progesterone receptor by binding to it. Estrogen and progesterone receptor share a common functional and structural organisation. Expression of progesterone receptor is a predictive marker and PR positive breast carcinoma is ER positive also.

Progesterone receptor was demonstrated by immunohistochemistry in formalin fixed paraffin section by Clarks et al. (1988).It is seen in the cells which are estrogen positive. Scoring system is also the same as for estrogen receptor.

SCORING SYSTEM

Estrogen and Progesterone receptor express positivity to nuclear staining. They are read by the proportion of the tumour cells expressing positivity and the intensity of the reaction. Both are added to obtain a score.

H – SCORE SYSTEM

It is a semiquantitative assay and was proposed by Goulding et al (1995). It is based on the different degree of relativity as shown by tumour cells. A score of 0 – 3 was given.

0 – No reaction

1 – Weak reaction

2 – Moderate reaction

3 – Strong reaction

Score calculation = % weakly positive cells x 1 +

% moderately positive cells x 2 +

% strongly positive cells x 3

Total score is between 0–300. Positive score is 51–300 and the negative score is upto 50 or less. The main disadvantage is time consuming and is impractical for the pathologists.

QUICK SCORE SYSTEM

This score is based on the proportion of the stained cell and the intensity of the staining. It was proposed by Barnes et al.(1998).

PROPORTION OF STAINING	**INTENSITY OF STAINING**
0 = No nuclear staining	0 =No staining
1 = < 1% nuclei staining	1 = Weak staining
2 = 1 – 10% nuclei staining	2 = Moderate staining
3 = 10 – 33% nuclei staining	3 = Strong staining
4 = 33 – 66% nuclei staining	
5 = 66 – 100% nuclei staining	

The total score is 8. When the score is more than 2 it is considered as positive. Advantage of the score is it predicts the probability of the response to hormone therapy

Experience to date suggests that using a simple scoring system will predict the values for treatment.

Score of 0 indicates that endocrine therapy will not work.

Score of 2 – 3 indicates 20% chance of response to therapy.

Score of 4 – 6 indicates 50% chance of response.

Score of 7 – 8 indicates 75% chance of response.

Where progesterone receptors content has been determined, endocrine therapy is deemed worthwhile with low ER but high PR.

HER-2/neu RECEPTORS

HER-2 /neu or c-erb-2 is the second member of the type 1 tyrosine kinase family. It encodes a transmembrane glycoprotein that is overexpressed in tumour cells. This proto oncogene is encoded by 17q11.2-q12. It belongs to EGFR family. Gene amplification is associated with poor prognosis. It can be detected by Florescent In Situ Hybridisation (FISH) and by immunohistochemistry for the protein overexpression. IHC is easy to perform and is cost effective than FISH.

SCORING SYSTEM

Staining pattern	Score	HER-2/neu expression
No staining or membrane staining in <10% of cells	0	Negative
A faint staining only a part of membrane >10% of cells	1 +	Negative

A weak to moderate complete staining in >10% of cells	2 +	Weakly positive
A strong complete membrane staining >10% of tumour cells	3 +	Strongly positive

ADVANTAGES OF ASSESSMENT OF ER / PR RECEPTORS IN BREAST CARCINOMA

1. For tumour behaviour in breast carcinoma Estrogen and Progesterone receptors are strong predictive and weak prognostic factors.

2. ER / PR positive tumours show response to hormone therapy in 50 – 60% of cases.

3. ER / PR positive tumours are associated with reduced risk of mortality and recurrence.

4. ER / PR negative tumours show very poor response to endocrine therapy.

MATERIALS AND METHODS

This is an analytical study done during the period from January 2013 to October 2013. It is conducted to female patients presented with a breast lump in the female OPD, The department of General surgery, Govt. Stanley Hospital, Chennai.

Female patients with palpable lump are admitted and are subjected to detailed history regarding age, parity, family history, socio economic status, menstrual history, lactational history and any previous biopsy reports if any.

Newly diagnosed patients and with unilateral breast malignancies, with no history of neoadjuvant chemotherapy are included in this study. Patients with bilateral breast malignancies and has a history of neoadjuvant chemotheroy are excluded from this study.

Based on the clinical examination, patients are subjected to mammogram, fine needle aspiration cytology (FNAC). If FNAC is proven to be inconclusive, trucut biopsy was done.

Based on the results of triple assessment if proven to be malignant, staging work-up done with X-Ray chest, Ultrasonogram of abdomen and pelvis and Bone scan (locally advanced breast carcinoma).

Based on the above findings patients are categorised as

1. Early Breast carcinoma (T1, T2, N1, N0).

2. Locally Advanced Breast Carcinoma (TxN2, T3Nx, T4Nx)

In Early breast cancer patient is subjected to MRM. The specimen is sent for histopathological study and hormone receptor study. Based on the histopathological report and hormone receptor status, patient is followed up with adjuvant chemotherapy and radiotherapy.

In Locally advanced breast carcinoma patient is subjected to trucut biopsy and the specimen is sent for histopathological study and hormone receptor status.

Based on the report patient is started on neoadjuvant chemotherapy followed by MRM. Postoperatively patient is started with chemotherapy/ radiotherapy.

Immunohistochemical analysis of hormone receptors are done in formalin fixed paraffin wax embedded tissue sections using the

Supersensitive Polymer HRP system which is based on non- biotin polymeric technology. It makes use of Super enhancer and poly HRP reagent. Then the retrieved antigen binds to primary antibody and then a secondary antibody conjugated with horse radish peroxidase polymer and DAB substrate is added for its detection. Then the score is calculated after required colour developed which can be read under a light microscope

OBSERVATION AND RESULTS

TABLE 1.

DISTRIBUTION OF BENIGN AND MALIGNANT BREAST TUMOURS.

S.NO	PERIOD	BENIGN TUMOURS	MALIGNANT TUMOURS
1	Jan 2013 – Oct 2013	73	50

TABLE 2.

AGE WISE DISTRIBUTION OF THE TUMOURS

S.NO	AGE (IN YEARS)	BENIGN TUMOURS	MALIGNANT TUMOURS
1.	Less than 20 Yrs	18	0
2.	21 – 30 Yrs	35	3
3.	31 – 40 Yrs	12	7
4.	41 – 50 Yrs	7	21
5.	51 – 60 Yrs	1	14
6.	61 and above	0	5
	Total No.of cases	73	50

Table 2 shows the distribution of breast tumours according to age. Benign tumours had a peak incidence in the age group 21 – 30 years, where as the malignant tumours had a peak incidence in the age group of 41 – 50 years.

TABLE 3.

DISTRIBUTION OF HISTOLOGICAL VARIANTS IN BREAST CARCINOMA

S.No.	Histological variants	No.of Cases	Percentage
1.	Invasive Ductal Carcinoma – NOS type	47	94%
2.	Invasive Lobular Carcinoma	2	4%
3.	Mucinous Carcinoma	1	2%
	Total No.of Cases	50	100%

Table 3 shows the distribution of histological variants in breast carcinoma. Among the 50 cases, 47 cases (94%) were Invasive Ductal Carcinoma Nos type, 2(4%) were Invasive Lobular carcinoma and 1 (2%) was Mucinous carcinoma.

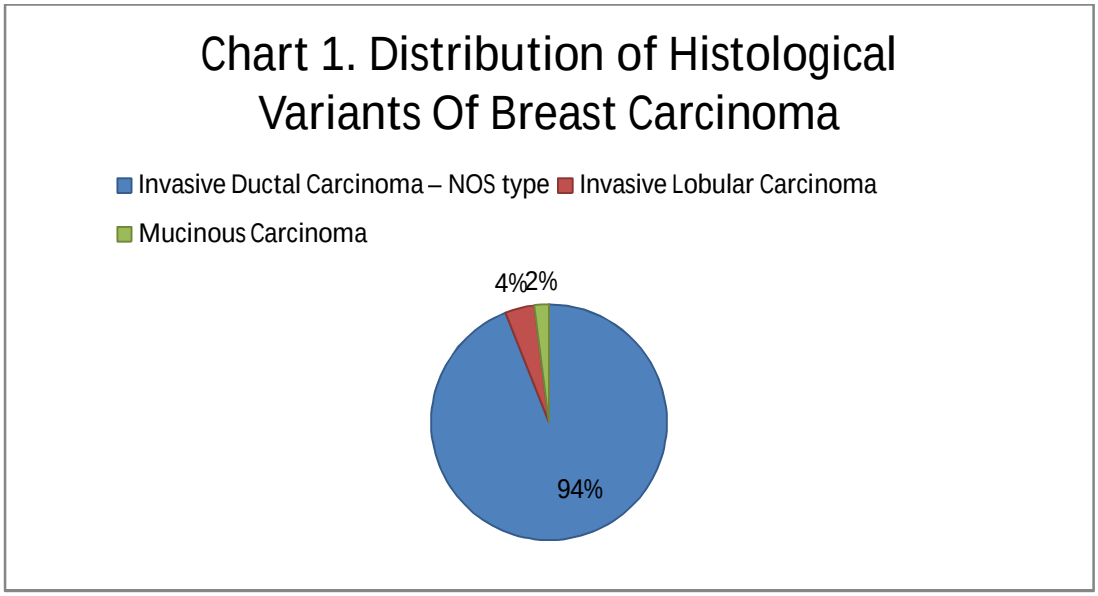


TABLE 4.

DISTRIBUTION OF HISTOLOGICAL GRADE IN INVASIVE DUCTAL CARCINOMA - NOS TYPE.

S.No.	Histological Grade	No.of Cases	Percentage
1.	Grade I	8	17%
2.	Grade II	33	70%
3.	Grade III	6	12%
	Total No.of Cases	47	100%

Table 4 shows the distribution of histological grading in breast carcinoma according to Modified Bloom Richardson scoring system. Only 47 cases were included for grading, in that 8 (17%) cases were in grade I , 33 cases (70%) were in Grade II, 6 cases (13%) were in Grade III.

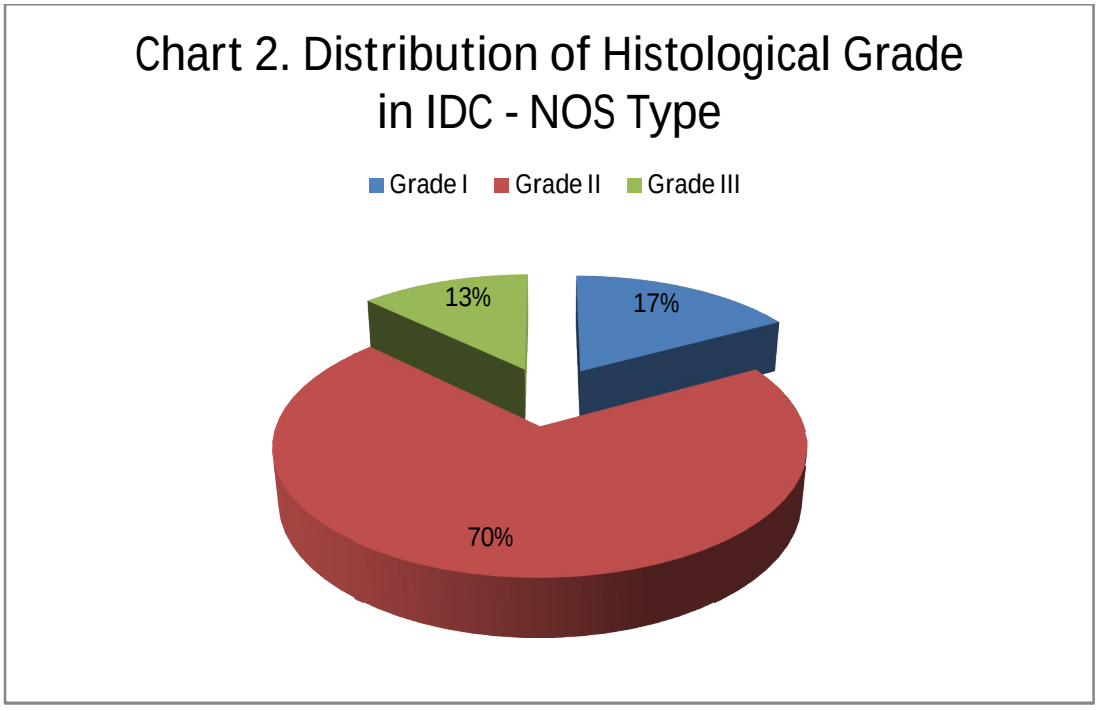


TABLE 5.

CORRELATION OF ESTROGEN RECEPTOR WITH PROGESTERONE RECEPTOR

S.No	Group	No.of Cases	Percentage
1.	ER+/PR+	22	44%
2.	ER-/PR+	9	18%
3.	ER+/PR-	4	8%
4.	ER-/PR-	15	30%
	Total No.of Cases	50	100%

Table 5. shows correlation of Estrogen receptors and Progesterone receptors. Among the 50 cases 22 cases were positive for both Estrogen and Progesterone receptors, 9 cases positive for progesterone receptor, 4 cases positive for estrogen receptor, while 15 cases were negative for both estrogen and progesterone receptors.

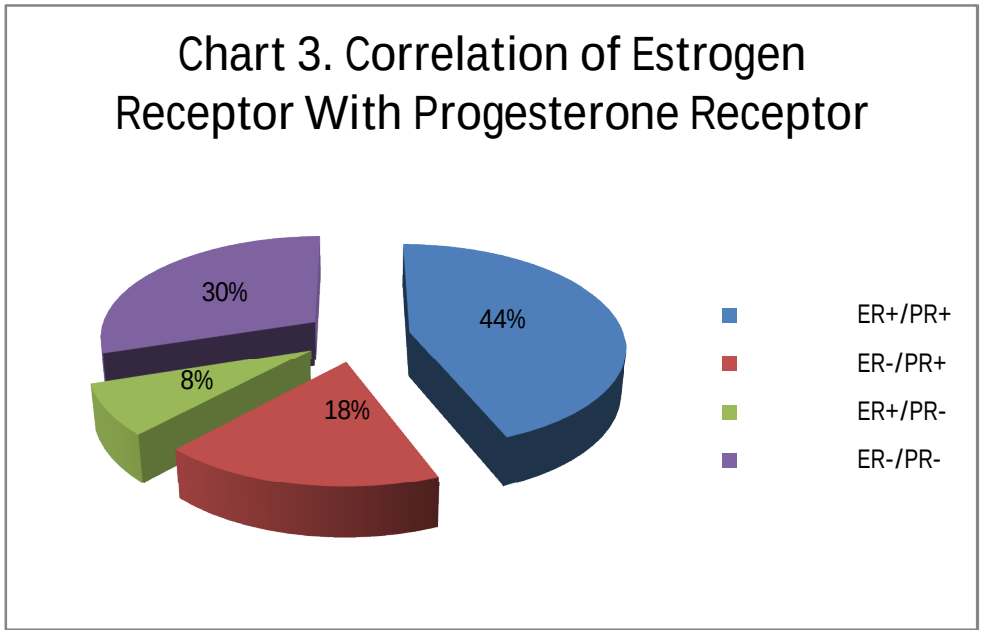


TABLE 6.

EXPRESSION OF HER-2/neu IN BREAST CARCINOMA

S.No	HER-2/neu expression		Total No. of cases	Percentage
1.	Positive	18	50	36%
2.	Negative	32		64%

Table 6. shows HER-2/neu overexpression in 50 cases of breast carcinoma, among them 18 cases (36%) were found to be positive, while 32 cases (64%) were found to be negative.

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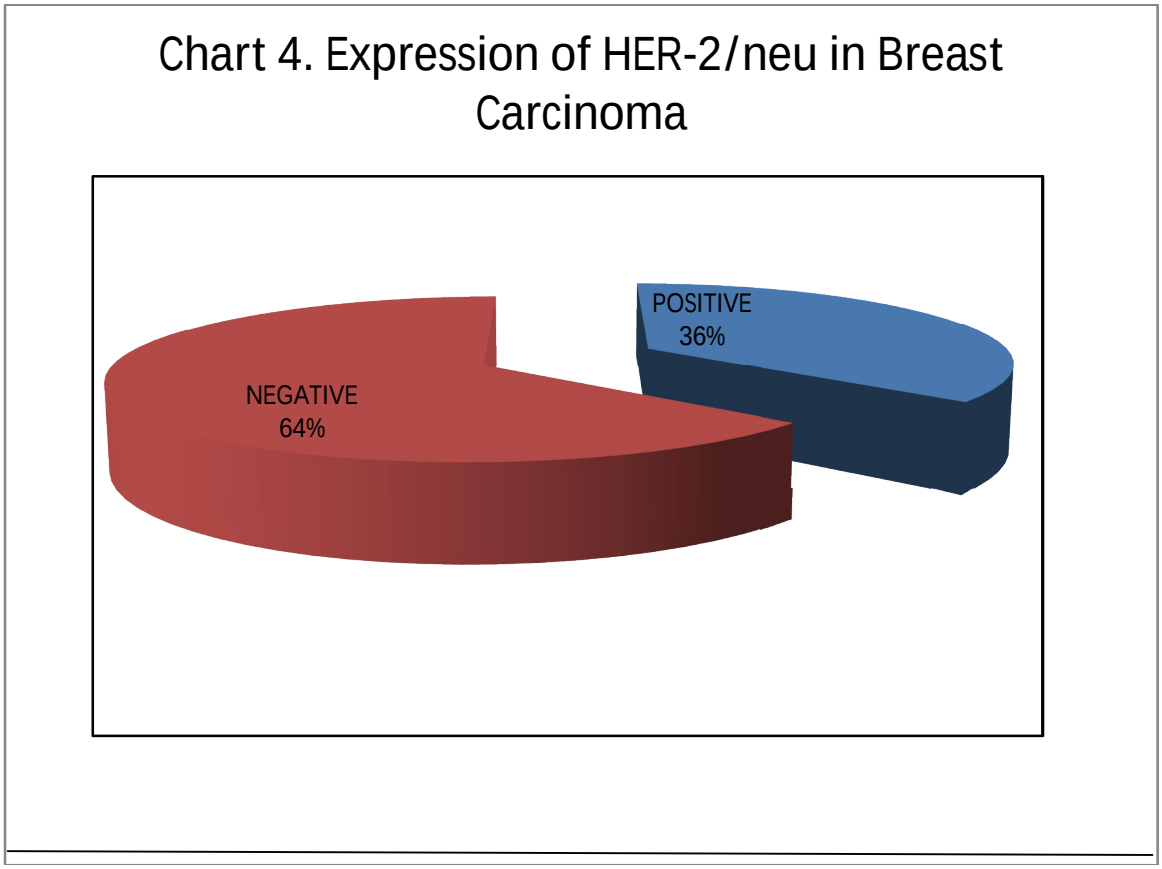


TABLE 7.

CORRELATION OF TUMOUR SIZE WITH HORMONE RECEPTORS

S.No	Tumour Size	Total	ER/PR Positive	Percentage
1.	T_1 < 2 cm	7	6	85%
2.	T_2 2 – 5 cm	17	16	94%
3.	T_3 > 5 cm	26	13	50%
	Total No.of Cases	50	35	

Table 7. shows correlation of hormone receptors with tumour size. Estrogen receptor and Progesterone receptor positivity was noted in 85% of T_1 sized tumours, 94% of T_2 sized tumours and 50% of T_3 sized tumours. The receptor status was found to be comparatively reduced in larger sized tumours as depicted. The correlation of hormone receptor with tumour size was statistically found to be significant (p=0.003).

Chart 5.

CORRELATION OF TUMOUR SIZE WITH HORMONE RECEPTORS

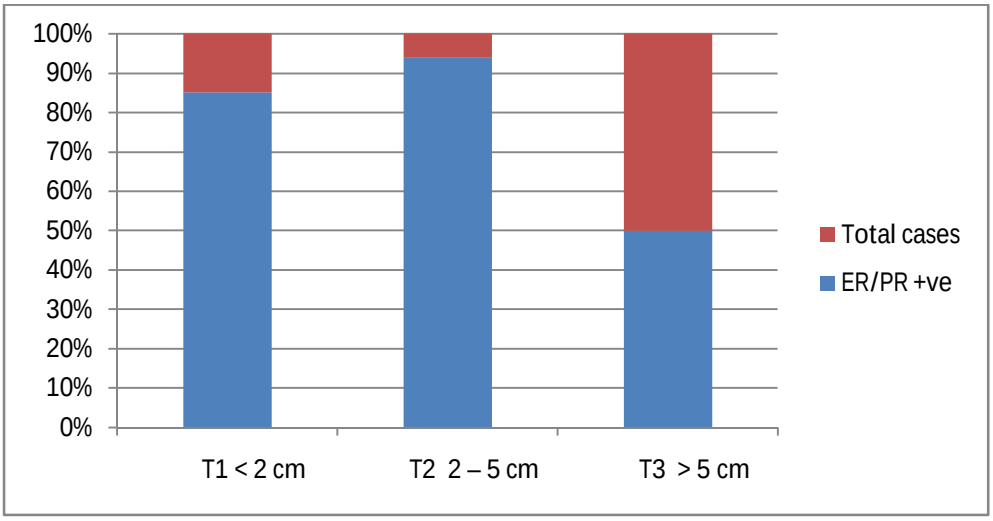


TABLE 8.

CORRELATION OF HER-2/neu WITH TUMOUR SIZE

S.No.	Tumour size	HER-2/neu positive	Total cases	Percentage
1.	<2 cm	1	7	14%
2.	2 – 5 cm	5	17	23%
3.	> 5 cm	14	26	53%

Table 8. shows correlation of HER-2/neu with tumour size. HER-2/neu overexpression was noted in 14% of T1 sized tumour, 23% in T_2 sized tumour and 53% in T_3 sized tumour. HER-2/neu overexpression was found in increasing size of the tumour.

Chart 6.
CORRELATION OF HER-2/NEU EXPRESSION WITH TUMOUR SIZE

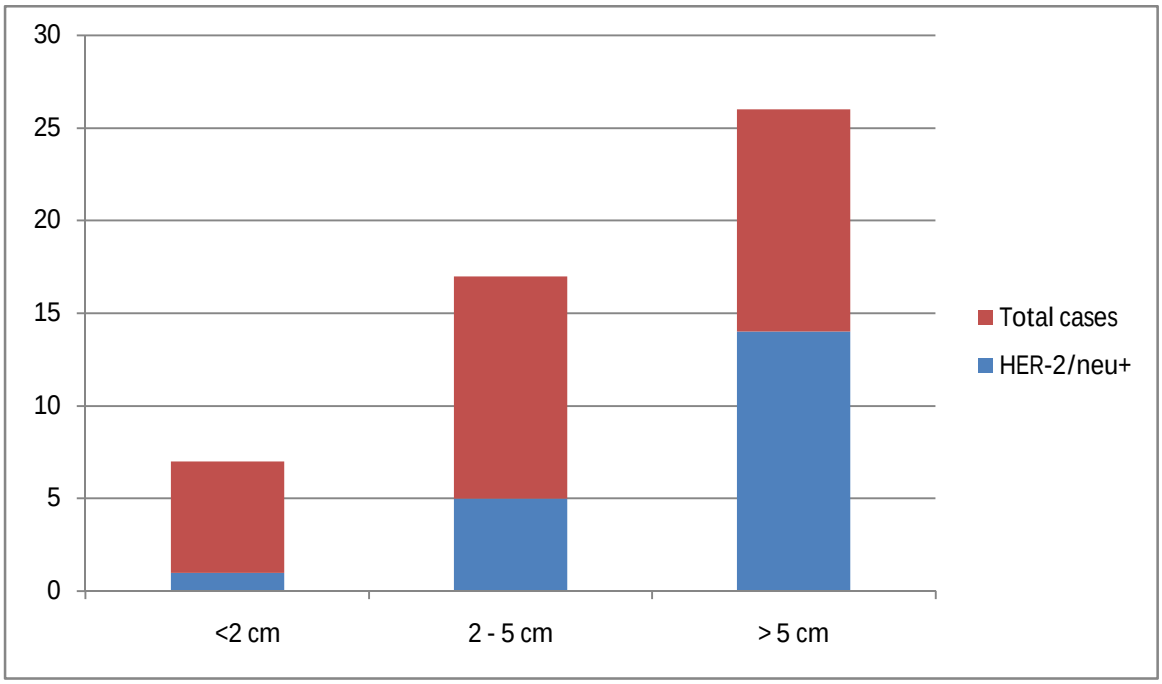


TABLE 9.

CORRELATION OF RECEPTOR STATUS WITH HISTOLOGICAL GRADING

S.No	Histological grade	Total No. of cases	ER/PR Positive	Percentage
1.	Grade I	8	8	100%
2.	Grade II	33	23	69%
	Grade III	6	2	33%

Table 9. shows correlation of hormone receptor status with tumour grade. Estrogen, Progesterone receptor positivity was seen in 100% in grade I tumours, 69% in grade II tumours and 33% in grade III tumours. This implies that high histological grade tumours showed low expression of receptor status.

CHART 7.

CORRELATION OF RECEPTOR STATUS WITH HISTOLOGICAL GRADE

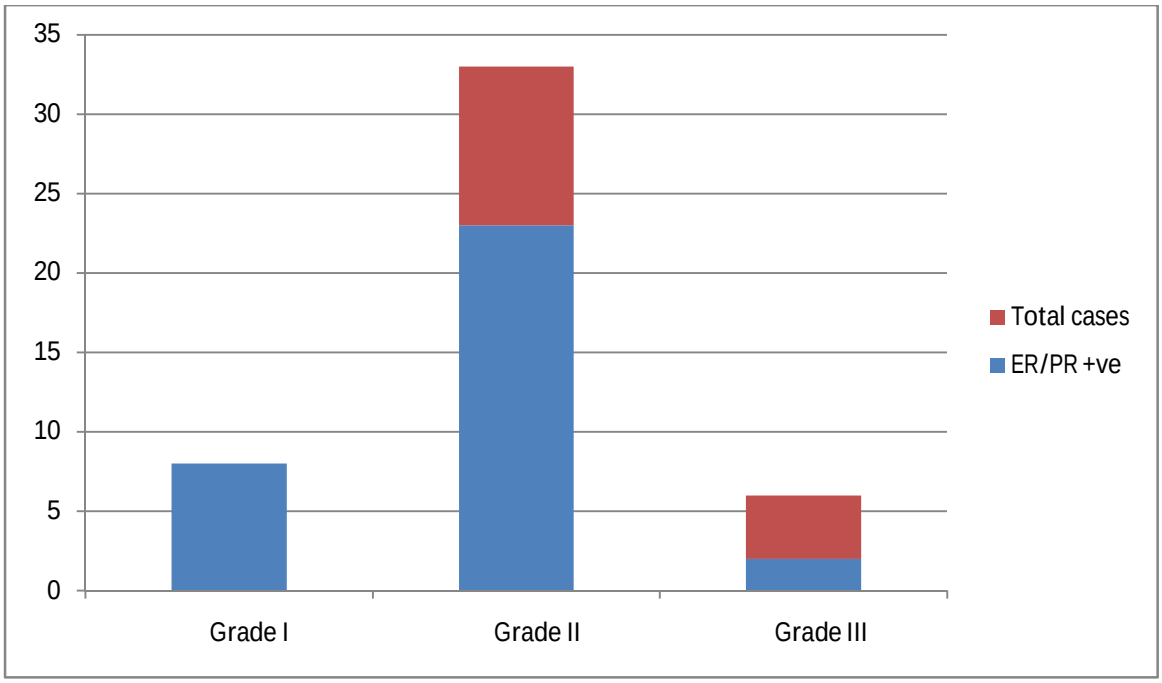


TABLE 10.

CORRELATION OF HER-2/neu WITH HISTOLOGICAL GRADING

S.No	Histological grade	HER-2/neu positive	Percentage
1.	Grade I (8 cases)	0	0
2.	Grade II (33 cases)	11	33%
3.	Grade III (6 cases)	4	66%

Table 10. shows correlation of HER-2/neu with histological grade. It was found that HER-2/neu overexpression was not seen in grade I tumours, where as it was expressed in 33% of grade II tumours and 66% of grade III tumours. Stastistically found to be significant (p=0.001).

CHART 8.

CORRELATION OF HER-2/neu WITH HISTOLOGICAL GRADING

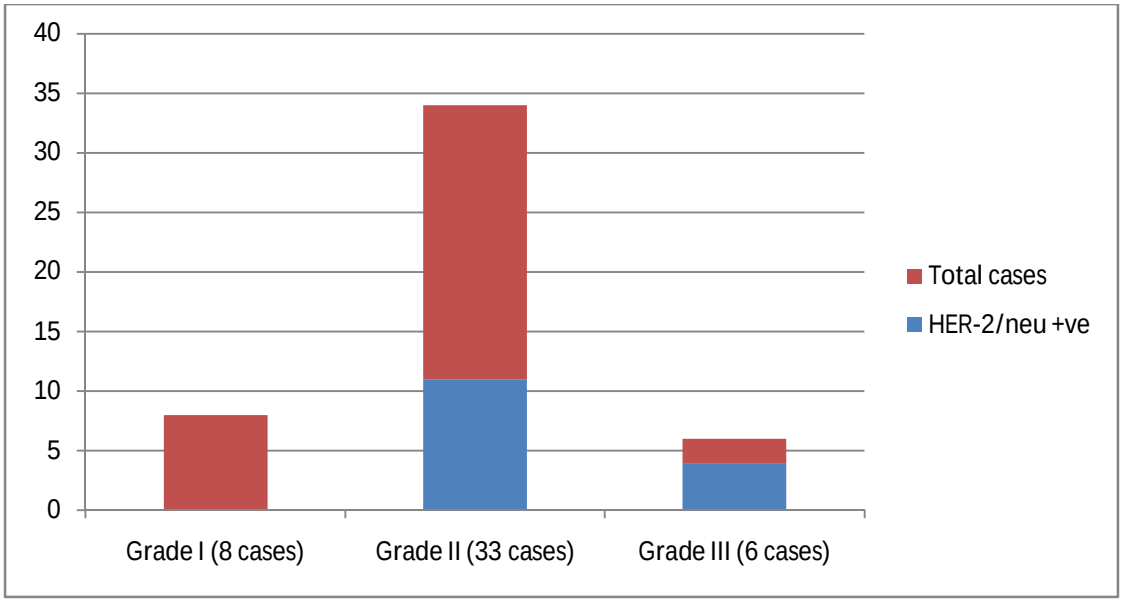


TABLE 11.

CORRELATION OF RECEPTOR STATUS WITH NODAL STATUS

S.No	Nodal metastasis	ER/PR positive	Percentage
1.	Present (17 cases)	9	52%
2.	Negative (29 cases)	21	72%

Table 11. shows correlation of hormone receptors with nodal status. Out of 46 patients 17 had nodal metastasis, among whom 9 showed receptor positivity. Out of 29 nodal negative patients, receptor status was positive in 21 patients. This explains higher receptor expression in nodal negative patients. Statistically found to be significant (p=0.001).

CHART 9.

CORRELATION OF RECEPTOR STATUS WITH NODAL STATUS

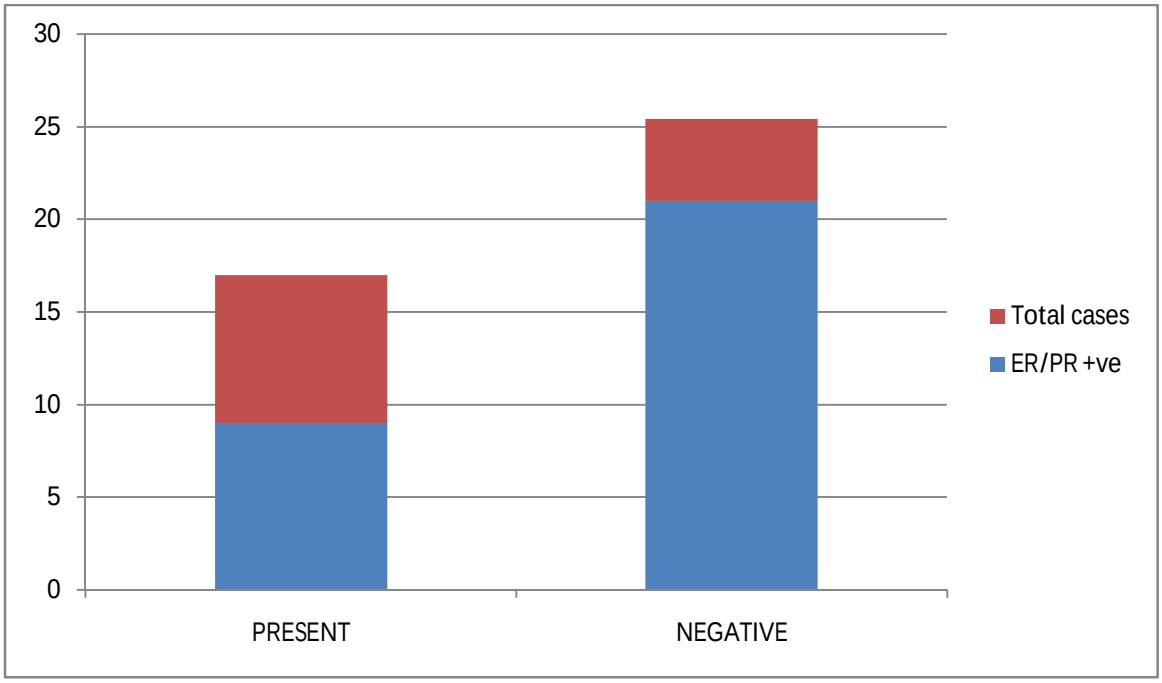


TABLE 12.

CORRELATION OF HER-2/neu WITH NODAL STATUS

S.No	Nodal metastases	HER-2/neu positive	Percentage
1.	Present (17 cases)	11	64%
2.	Negative (29 cases)	2	6%

Table 12. shows correlation of HER-2/neu with nodal status. Out of 46 cases, HER-2/neu overexpression was seen in 64% of nodal positive patients as opposed to 6% of nodal negative patients. Statistically found to be significant (p=0.001).

CHART 10.

CORRELATION OF HER-2/neu WITH NODAL STATUS

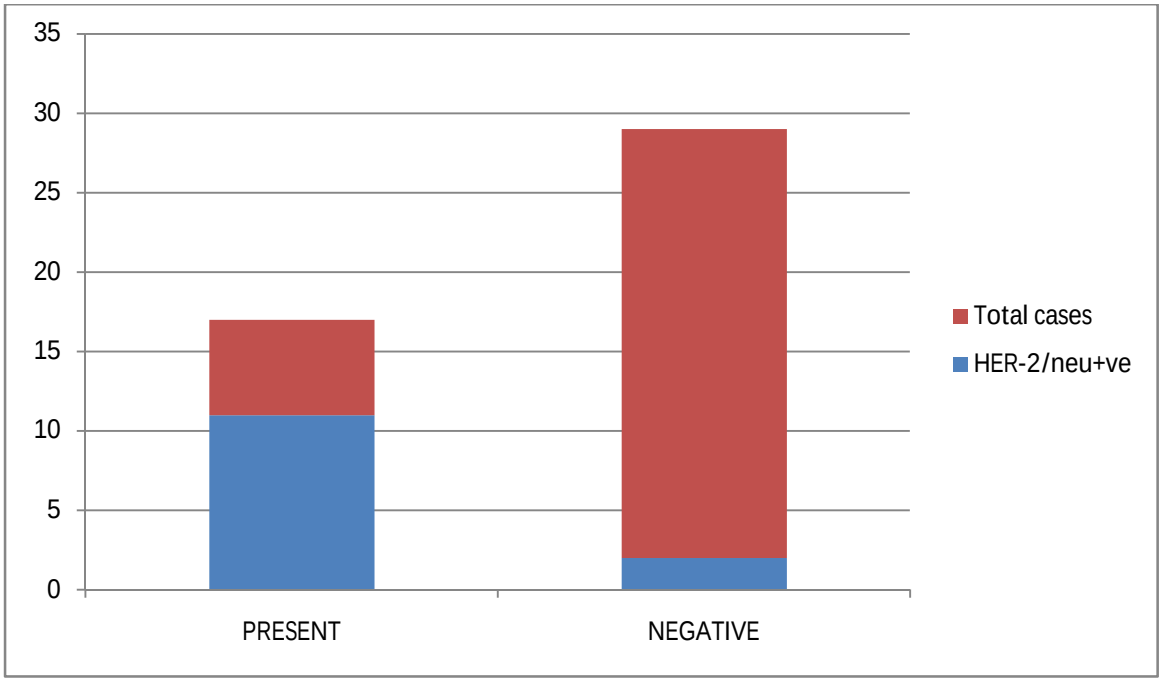


TABLE 13.

CORRELATION OF RECEPTORS WITH ONCOPROTEIN EXPRESSION

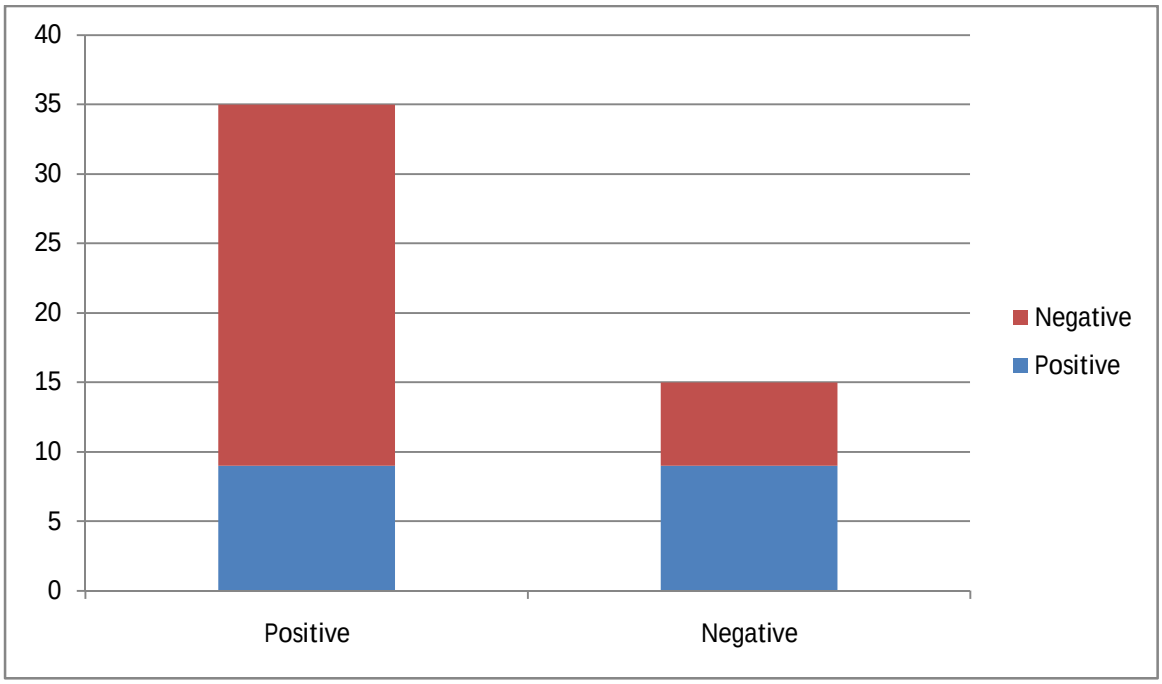
ER/PR Status	HER-2/neu		Total No. of cases
	Positive	Negative	
Positive	9	26	35
Negative	9	6	15
Total No. of cases	18	32	50

Table 13. shows an inverse relationship of estrogen, Progesterone receptor status with the HER-2/neu status.

Statistical analysis was performed and found to significant (p=0.001).

CHART 11.

CORRELATION OF RECEPTORS WITH ONCOPROTEIN EXPRESSION



DISCUSSION

INCIDENCE AND AGE OF OCCURRENCE:

In Indian scenario, breast carcinoma accounts for 33% of all female cancers and 20% of cancer related deaths in women. In Chennai breast cancer accounts for 26.8% of all cancers in women. A few decades back breast carcinoma is more common in women above 50 years comprising about 65% to 70% with 30% to 35% of women were below 50 years of age. But at present the scenario has changed with increasing incidence between 41- 50 years of age comprising of about 49%. Breast cancer scenario in India also shows a significant trend of increased incidence of breast cancer in much younger age than earlier.

In accordance with the above mentioned studies, the present study also revealed that the distribution of the disease has a peak age occurrence of 41 – 50 years age group.

TABLE 14.

COMPARATIVE ANALYSIS OF DISTRIBUTION OF HISTOLOGICAL VARIANTS OF BREAST CARCINOMA

Histological Types	Dixon JM et al.	Omar Hameed	Current study
IDC – NOS type	79%	>70%	>70%
Lobular carcinoma	10%	5 – 15%	4%
Mucinous carcinoma	2%	1 – 5%	2%
Medullary carcinoma	2%	1 – 7%	0
Papillary carcinoma	1%	2%	0
Solid neuroendocrine	<1%	Rare	0
Metaplastic ca	0	2-5%	0

Table14. shows the comparative analysis of the distribution of histological variants of breast carcinoma. The incidence encountered by Dixon et al and Omar Hameed et al. were comparable with the present study. The most common histological type in concurrence with the other results was Invasive ductal carcinoma – NOS type.

THE IDENTIFIABLE HISTOLOGICAL VARIANTS ARE AS FOLLOWS

1**. INVASIVE DUCTAL CARCINOMA –NOS TYPE:**

This is the largest group of malignant tumours accounting to 65-80% of breast carcinoma . Our study shows 94% distribution. Grossly the tumour size varied from 2cm to 12 cm. Cut section of most of the tumour showed gray white, ill-defined tumour mass, firm to hard in consistency. Occasionally tumour showed areas of hemorrhage and necrosis. Microscopically the neoplastic cells were arranged in diffuse sheets,nests and cords along with glandular and tubular differentiation. In few cases comedo - pattern of necrosis was seen. About 40 percent of the cases (17/43) showed nodal metastasis. Most of the tumours were found to be in histological grade II. Resected margin involvement was seen in two patients and was confirmed by microscopic examination.

2. **INVASIVE LOBULAR CARCINOMA**:

An incidence of 4.9 -12% in post menopausal age group was recorded by Foot and Stewart. In the present study this variant represented 4% of occurrence. The peak age of occurrence is 41 - 45 years. Grossly the tumour was gray white, firm measuring 6cms in diameter. Microscopically “Indian file” pattern was noted. The cells were

small to medium sized with uniform, hyperchromatic nuclei, and mild nuclear pleomorphism. Microscopically, metastasis was found in 23 lymph nodes.

3**. MUCINOUS CARCINOMA**:

In Omar Hameed et al study incidence of Mucinous carcinomas was 5-15% and the mean age of occurrence was 58-68 years. The present study data represents 2% of distribution and the age of occurrence was 73years. This is parallel with above mentioned study. Grossly the tumour mass was about 6cm -10cm, well circumscribed with gelatinous appearance. On cut section soft, gel like material was noted. Microscopically clusters of bland appearing epithelial cells with abundant extracellular mucin were noted .

HORMONE RECEPTOR STATUS AND HER-2/NEU IN BREAST CARCINOMAS

Estrogen, Progesterone receptor positive tumours have a significantly longer disease free survival than with the receptor negative tumours. In 1975 Rosen et al. attempted to correlate Estrogen, Progesterone receptors status along with various histological types of

breast carcinoma. In his study Estrogen, Progesterone receptors were positive in 70-80% of the tumours and HER-2/ neu expression was positive in 15-20% of the breast carcinoma specimen.

In the year 1993, Wilbur D et al. did a study about hormone receptor status in 30 patients by immunohistochemical method on paraffin wax embedded blocks. He described Estrogen receptors positivity in 73% (22/30) of patients, Progesterone receptors positivity in 63% (19/30) of patients, and HER-2/neu overexpression in 37% (11/30) of patients.

In the year 2003 Lici et al. have reported about the incidence of invasive carcinoma by hormone receptor status from the year 1992 to 1998, in a population based study. He found that there is a increase in prevalence over the years with increase in hormone receptor positivity from 75.4% to 77.5% in United States.

The number of studies performed on the hormone receptor status is much less in Asian women when compared with western world. In the year 2000 Desai et al. documented the Estrogen, Progesterone receptors status of carcinoma breast in India. The study was done with the help of immunohistochemical method. He studied a total of 798 tumours, in that

32.6% were Estrogen receptor positive and Progesterone receptor positive were 46.1%. He reported a high incidence of hormone receptors non-reactivity in breast carcinoma patients in India.

In the year 2008 , Col.V. Dutta et al. did a study in Armed Forces Medical College, Pune. He analyzed the hormone receptors and HER-2/neu overexpression in breast carcinoma. In total of 75 tumours which was studied, 33% (25/75) of cases expressed Estrogen receptor positivity, Progesterone receptor or both where found to be negative in as 67% (50/75). HER-2/neu overexpression was seen in 58 %(43/75) of cases. This study revealed that receptor negativity is higher in this population of tumours when compared with the western communities.

In the year 2009, Lakmini K.B Mudduwa studied the hormone receptor status of breast carcinoma by using the Quick score method. She reviewed a total of 151 cases and documented the prevalence of Estrogen receptor positivity in 45.7% of the cases, Progesterone receptor positivity in 48.3% of the cases and both receptors negativity in 54.3% of the total cases. According to her study HER-2/neu overexpression was seen in 19.1% (26/136) of the total cases.

In the year 2009,Tanuja Shet et al. did a study on the hormone receptors expression in the last 8 years from the year 1999 to 2006 in a

cancer referral institute in India. A total of 11,780 cases were reviewed for this period. The percentage of hormone receptor positive expression varied from 52% to 57%.

In the year 2007, Vikash Kumar et al. did a study on HER-2/neu overexpression which has a much higher incidence among Indian breast cancer patients which is 46.3% in comparison to 25-30% in Western world.

In the present study Estrogen, Progesterone receptor or both were positive in 70% of cases and both receptors were negative in 30% of cases (Tab.5).

HER-2/neu overexpression was positive in 36% of cases (Tab.6). Hence this study is comparable with the studies conducted in the Asian communities. There appears to be a minimal variation in receptor expression;because technically this could be explained by the differences in the technique of evaluation and inter laboratory variations.

ESTROGEN, PROGESTERONE RECEPTOR AND HER-2/NEU STATUS IN HISTOLOGICAL VARIANTS

In the year 1975, Rosen PP et al. found that Mucinous carcinomas, Papillary carcinomas are Estrogen and Progesterone receptors positive

whereas Medullary carcinoma and Metaplastic carcinoma were both found to be hormone receptor negative. He has also found that a small group of Invasive ductal carcinoma-NOS type and Lobular carcinomas expressed receptor negativity.

In the year 2000, Desai et al. reported that Invasive lobular carcinoma, Mucinous carcinoma and mixed tumours were Estrogen and Progesterone receptor positive, where as high grade infiltrating ductal carcinomas, in situ comedo-ductal carcinomas ,Medullary carcinomas were found to be receptor negative.

The author Diab SG et al did a study on the tumour characteristics and clinical outcome of Mucinous and Tubular breast carcinomas and found Estrogen receptor positivity in 92% of cases and reported Progesterone receptor positivity in 68% of cases. HER-2/neu overexpression is found to be less than 5% of tumours. Similar results were also reported in studies conducted by Shousha S, et al. in the year 1989.

In the year1988, Reiner et al. found that Papillary carcinomas expressed 100% Estrogen receptor positivityand expressed 80% of Progesterone receptor positivity. They tend to have a HER-2/neu negativity .

In the year 1995, Rosen et al. did a study on HER-2/neu expression in nodal negative patients. He has also reported low incidence of oncogene expression in Papillary carcinomas.

In the year 1991, Soomro S et al. did a study about oncogene expression in different histological variants of invasive breast carcinomas and reported low expression in Neuroendocrine carcinomas.

Immunohistochemical studies done by LeeAK revealed Neuroendocrine marker positivity in 82% of the cases. However 67% expressed Estrogen receptor positivity and 56% showed Progesterone receptor positivity. However ,HER-2/neu over expression was found to be negative.

The present study also shows Estrogen and Progesterone receptor positivity and HER-2/neu expression negativity. This is in correlation with the above mentioned studies.

In the year 1987, Oberman HA et al. did a study which showed that Metaplastic carcinomas were hormone receptor and oncoprotein negative called as Triple negative.

In the year 1986, Horsfall et al. conducted a study on the relationship between DNA ploidy and steroid receptors. He found that

Medullary carcinoma has a higher nuclear grade with receptor negativity.

In the year 1995, a study conducted by Rosen PP et al. and Soomro S.et al. in the year 1991 showed a low incidence of HER-2/neu overexpression in Metaplastic and Medullary carcinoma.

In the year 1992,Kuenen–Boumeester V et al did a study on the immunohistochemistry of Androgen receptors in relation to the Estrogen and Progesterone receptors. He also reported that a small group of lobular carcinomas were found to express both receptors negativity and Androgen receptor positivity.

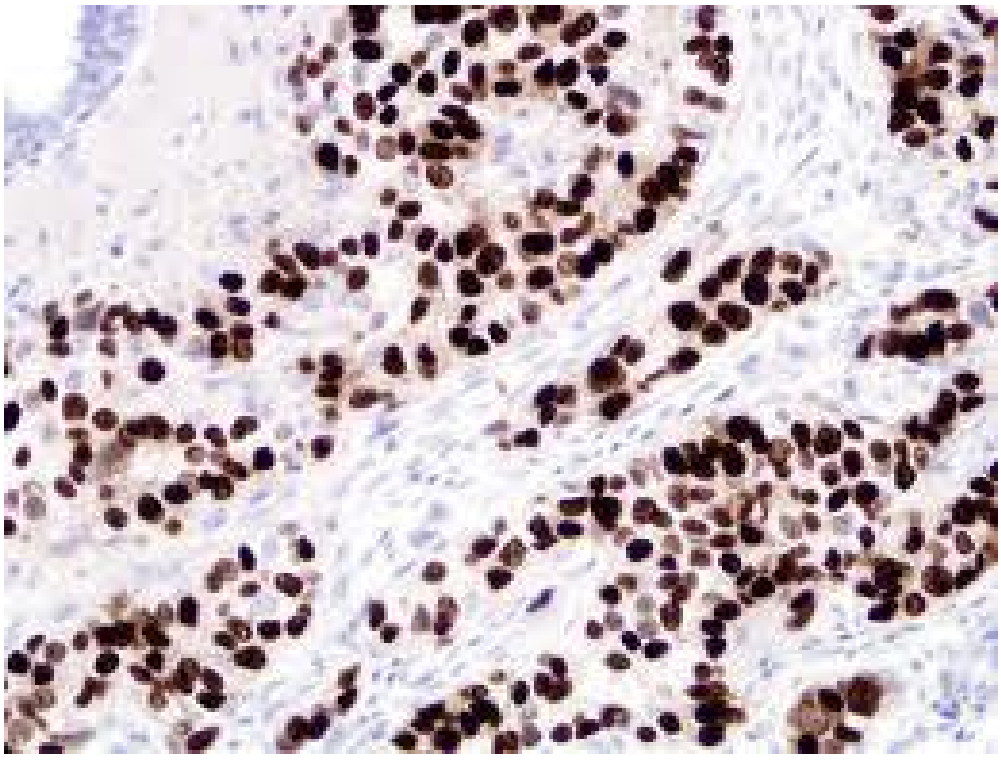
In the year 1995, a study conducted by Rosen PP et al. showed Estrogen receptor positivity in 87.55% of the cases and Progesterone receptor positivity in 75% of the cases in Invasive lobular carcinomas. A small group of these tumours also expressed both receptor negativity and Androgen receptor positivity.

In the year 2005, Riva et al studied about the immunhistochemical analysisof Androgen receptor in carcinoma breast and reported increased frequency of androgen receptor expression in

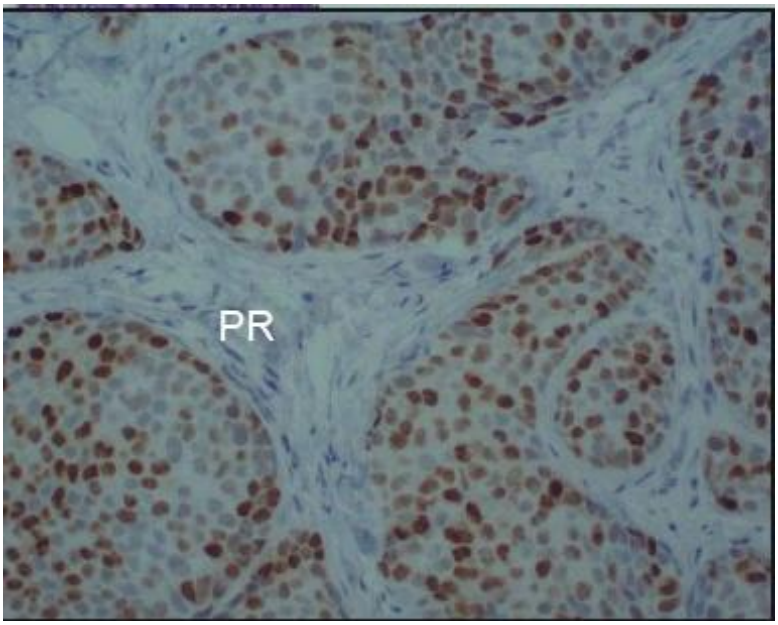
Lobular carcinomas along with Estrogen and Progesterone receptors negativity.

In correlation with the above mentioned studies the Invasive lobular carcinoma in the current study also expressed both receptors and HER-2/neu negativity. Clinicopathologically this can be explained by the aggressive nature of the tumour with higher incidence of nodal metastases.

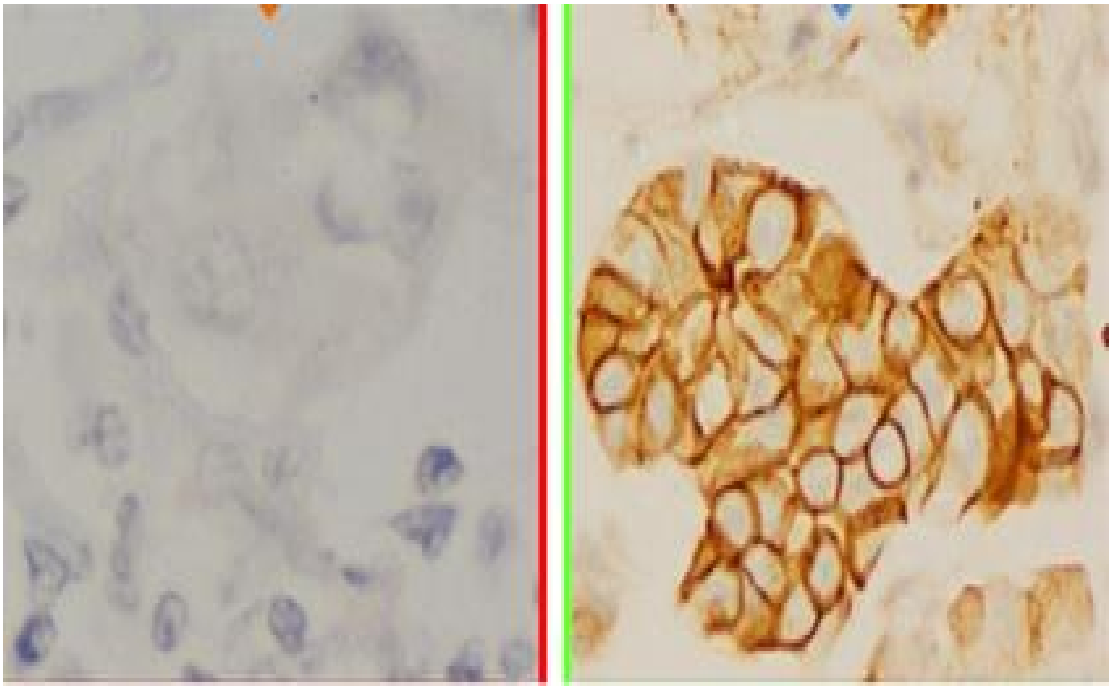
ER POSITIVE



PR POSITIVE



HER 2 / neu NEGATIVE **HER 2 / neu POSITIVE**



CORRELATION OF AGE AND RECEPTORS EXPRESSION

TABLE 15.

CORRELATION OF AGE AND RECEPTORS EXPRESSION.

Age group(years)	Total No. of cases	ER/PR positive
31 – 40	7	3
41 -50	21	14
51 – 60	14	11
60 and >	5	4

In the year 2008, Col.V. Dutta et al. studied about the Estrogen, Progesterone receptor expression with the age. Out of the total 75 cases, 35% of cases were in 51-60 years age group. The results showed that the receptor positivity increases with advancing age. Young patients tend to have a higher level of circulating estrogen and hence correspondingly low expression of receptors.

In the year 2005, Nidal M Almasri et al. reviewed about 91 specimens of breast carcinoma during the period of 1995-1999. He has found significant receptor expression in 58% patients older than 50 years.

The present study shows receptor status positivity of 78% in patients older than 50years of age group. The Increased immunoreactivity with advancing age is parallel to above the mentioned studies.

ESTROGEN, PROGESTERONE RECEPTOR, HER-2/NEU WITH OTHER VARIABLES

In the year 1995, Rosen PP et al. in his study correlated Estrogen, Progesterone receptor positivity with histological grade and tumour size. He concluded that Estrogen and Progesterone receptors are expressed more in the low grade and tumours which are of lesser diameter. He also reported that HER-2/ neu overexpression was increased among the nodal positive patients and tumours which are more than 2cm in diameter.

J.Buon et al. reported that HER-2/neu receptor overexpression is increased in higher grade tumours. Hormone receptor positivity was seen 100% in grade I tumours, 76.30% in grade II tumours and 41.18% in grade III tumours. Their receptor positivity tends to have an inverse relationship with the tumour grade.

In the year 2008, S.Goyle et al. conducted a retrospective study in India. He reviewed about 131 patients and found that the hormone

receptor and oncoprotein expression does not necessarily correlate with advanced grade tumours in our population.

In contrast with S.Goyle et al. in the year 2008 the present study showed the Estrogen, Progesterone receptor positivity of 100% in grade I, 69% in grade II, 33% in grade III tumours. HER-2 /neu overexpression showed 66% in grade III, 33% in grade II, none in grade I tumours. This explains the overexpression of oncoprotein with higher histological grade tumours. Thus, it reflected a direct relationship with higher nuclear grade, which was comparable with J.Buon et al & Rosen PP et.

Current study shows correlation of hormone receptors and HER-2/neu with tumour size.The tumours are categorized into three according to T in TNM staging. T1- < 2cm, T2=2-5cm, T3 = > 5 cm. Receptor positivity is expressed in 85% of T1, 94% of T2 and 50% of T3 tumours. This explains that receptor positivity has an inverse relationship with the tumour size.

HER-2/neu overexpression showed positivity in 14% of T1,23% in T2 and 59% in T3 tumours. This explains the higher expression of oncoprotein among the tumours of more than 2 cm size.

CORRELATION WITH NODAL STATUS

In the year 2008, Col.V. Dutta et al. expressed a strong correlation between HER-2/neu and nodal metastases. He reported that 70% of nodal positive tumors overexpressed HER-2/neu oncoprotein.

H.J. Huang et al. did a study in 1362 women with primary breast tumour. He found that Estrogen receptor positivity was expressed less in nodal positive tumours.

In the present study out of 46 patients 17 cases showed metastasis while 29 cases has no metastases. Receptor positivity was found to be higher among the nodal metastasis negative patients which was about 72% (21/29).HER-2/neu overexpression was seen in 64% of nodal positive cases than the nodal negative patients which was found to be 6 %.

CORRELATION OF ESTROGEN, PROGESTERONE RECEPTOR WITH HER-2/NEU

H.J. Huang et al. conducted a study in 1362 women with primary breast tumours. He has found an inverse relationship with hormone receptor and oncoprotein expression. This can be explained by the fact that there is cross-linkage between the two pathways of tumour growth.

The present study showed an inverse relationship between these hormone receptors and oncoprotein expression.Hence it is comparable with the above mentioned studies.

In the year 2006, Francis G et al. did a study of 591 tumours and concluded that more than 20% of HER-2/neu positive tumours showed moderate or strong staining for Estrogen receptors.

In the year 2009, Bhargava R et al. has reviewed about 205 cases and concluded that 15% (32/205) of the cases were triple negative, 4% (8/205) of cases were positive for Estrogen receptor and HER-2/neu hybrid oncoprotein expression.

In correlation with the above mentioned studies the present study also showed a inverse relationship with hormone receptor and oncoprotein expression.

SUMMARY AND CONCLUSION

- The benign lesions had a peak occurrence in the age group 21 to 30 years, whereas malignant tumours had a peak in the age group 41 to 50 years.

- Among the various histological variants in breast carcinoma, Invasive Ductal carcinoma – NOS type constituted about 94% of cases.

- Estrogen, Progesterone receptor positivity and HER-2/neu negativity in Mucinous carcinomas.

- Triple negativity in small group of Invasive lobular carcinoma.

- Regarding the histological grade of breast carcinoma, Grade II tumours were common accounting for 70 %.

- Estrogen and Progesterone receptor or both was found in 70% while 30% were found to be receptor negative.

- HER-2 /neu overexpression was found to be positive in 36% of tumours and it was negative in 64% of tumours.

- Out of the total 50 cases, 26 cases were T3 tumours of more than 5cms in diameter.

- Larger the tumour size lesser is the expression of hormone receptor, whereas smaller sized tumours expressed more receptor positivity. This inverse correlation was statistically significant (P=0.003). HER-2/neu overexpression was found in tumours of more than 2 cm in size.

- Among the 46 cases, nodal metastasis were found in 17 cases and negative in 29 cases.

- Among the 29 nodal negative patients Estrogen, Progesterone receptor were positive in 21 cases. Thus, there is higher receptor expression in nodal negative patients. This was found to have a significant correlation (P=0.001).

- HER-2/neu overexpression was observed in 64% of nodal positive patients, which is statistically significant (P=0.001).

- Higher the histological grade of breast carcinoma, lower the receptor positivity. 33% of the grade III tumours expressed receptor positivity in comparison to 100% in grade I tumours.

- Higher the histological grade of breast carcinoma, greater the HER-2/neu overexpression, which was found to have a significant correlation (P=0.001).

- Higher the Estrogen, Progesterone receptor positivity, lower was the HER-2/neu overexpression. Thus, there was an inverse relation between the receptor and HER-2/neu, which was found to be statistically significant (P=0.001).

CONCLUSION

Estrogen, Progesterone receptor positive tumours are more common in the post menopausal women, tumours of more than 2cm in size, Histological grade I and in nodal negative patients. Oncoprotein overexpression is common among the tumours of more than 2cm in size, grade III tumours and in nodal positive patients. Hormone receptor and oncoprotein expression has an inverse correlation with each other.

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INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Harmone receptor status in breast cancer in relation to histological grading, Age and lymphnode involvement

Principal Investigator : Dr.R.Rani Suganya

Designation : PG in M.S.(Gen.Sur)

Department : Department of General Surgery
Government Stanley Medical College,
Chennai-10

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 13.06.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

13/12/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI

PROFORMA

- NAME : SL. NO:
- AGE /SEX:
- ADDRESS WITH CONTACT NUMBER:
- IP NO:
- DATE OF ADMISSION:
- DATE OF SURGERY:

HISTORY OF PRESENTING ILLNESS:

Lump

- Duration
- Onset
- Rate of growth

Pain

- Character and features of pain
- Relation to menstruation

Discharge from nipple

- Duration
- Quality- nature, color, odour.
- Quantity.

Retraction of nipple

H/o of trauma

H/o loss of weight/appetite

H/o of bone pain

H/o of jaundice

H/o of breathlessness

H/o of cough with hemoptysis.

PAST HISTORY :

H/o DM, HT,TB,Asthma,epilepsy.

H/o any previous surgery

H/o of drugs/ oral contraceptives.

FAMILY HISTORY:

Family history of Breast carcinoma, ovarian tumors, uterine tumors.

PERSONAL HISTORY:

Age at menarche, childbirth.

Marital status

Breastfeeding

Age at Menopause.

TREATMENT HISTORY:

SYSTEMIC EXAMINATION:

CVS

RS

PER ABDOMEN

CNS

EXAMINATION OF BREAST

INSPECTION

1.Inspection of the patient in sitting posture, arms by the side of her body

- Breast
- Skin over the Breast
- Nipple
- Areola
- Arms and Thorax
- Axilla
- Supraclavicular fossa

2. Inspection of the patient with arms raised above head

- Peau de orange present/absent.
- Fixity present/absent
- Retraction of nipple

3. Inspection on leaning forward

- Fixity to chest wall

4.Inspection on contracting and relaxing pectoralis major.

- Swelling becomes prominent or not

PALPATION

1.Local temperature and tenderness.

2.Swelling

3.Fixity to skin

4.Intrinsic mobility.

5.Fixity to chestwall

6.Fixity to muscles.

EXAMINATION OF AXILLARY LYMPHNODES

Examination of other Breast,opposite axilla, supraclavicular fossa.

PR/PV.

DIAGNOSIS:

INVESTIGATIONS

CBC

RFT

LFT

X-RAY chest

ECG

USG/ Mammogram

FNAC

Trucut Biopsy

IHC- ER,PR,HER 2/neu

SURGERY DONE:

HPE REPORT

MASTER CHART

S.NO	NAME	IP NO	AGE (YRS)	HPE NO.	CYTOLOGY NO.	PROCEDURE DONE	STAGE	TUMOUR SIZE(cm)
1	CHINNAMMAL	8276	75	416/13	542	Rt MRM	T4bN0M0	12*10*3
2	RAMZAN BEE	7412	53	495/13	598	Lt MRM	T2N0M0	3*3*2
3	CHANDRA	7812	46	514/13	613	Rt MRM	T2N0M0	2.5* 2* 2
4	VICTORIA	1936	50	649/13	217	Lt MRM	T4bN0M0	8*5*4
5	KALAISELVI	4357	56	739/13	289	Lt MRM	T3N0M0	6*4*2
6	KUMARI	2452	76	766/13	227	Lt MRM	T1NOMO	2*2*1
7	OMANA	3910	61	666/13	509	Rt MRM	T1N0M0	2*2*1
8	KAMATCHI	7382	56	1050/13	865	Rt TRUCUT	T4BN0M0	6*5*3
9	SHAMIRA	8787	40	1119/13	466	Lt TRUCUT	T4BN0M0	7*5*3
10	VIJALAKSHMI	8826	26	1128/13	897	Lt TRUCUT	T3N1M0	6*5*3
11	KALA	7152	35	1202/13	789	Rt MRM	T3 N0M0	6*4*3
12	LALITHA	6573	50	1338/13	801	Rt MRM	T2N1M0	3*2*2
13	RAVANAMMA	12149	41	1608/13	946	Lt TRUCUT	T3N1M0	6*5*4
14	NAGAMMAL	11823	55	1818/13	1012	Lt MRM	T1N2M0	2*2*1
15	SAKKAMMA	11487	60	1887/13	1021	Rt MRM	T2N0M0	3*3*2
16	YASODHA	12511	54	1934/13	1212	Lt MRM	T2N0M0	4*3*2
17	VIJAYA	14282	35	1935/13	1232	Lt MRM	T3N0M0	6*5*3
18	KANAGA	21483	45	2796/13	1453	Lt MRM	T2N0M0	4*3*3
19	RADHA	22400	60	2822/13	2040	Lt MRM	T4bN1M0	5*4*3
20	GNANASELVAM	23145	56	2839/13	2105	Rt MRM	T3N1M0	5*4*4
21	PREMA	24057	53	2871/13	2112	Rt MRM	T2N1M0	4*3*2

22	FATHIMA	24518	48	2917/13	2219	Lt MRM	T3N1M0	6*5*4
23	MOHANA	25178	35	3131/13	2561	Lt MRM	T4bN1M0	7*4*3
24	PARIMALA	25217	53	3212/13	2781	Rt MRM	T3N1M0	6*5*4
25	KAVYA	26711	39	3617/13	2889	Lt MRM	T1N0M0	2*2*2
26	MALATHY	29010	44	3913/13	3131	Rt MRM	T3N1M0	7*5*4
27	BANU	31145	51	4131/13	3211	Lt MRM	T3N0M0	6*5*3
28	LAVANYA	32121	44	4191/13	3231	Lt MRM	T2N0M0	4*4*3
29	MARIAMMAL	32213	43	4277/13	3421	Rt MRM	T4bN1M0	7*6*4
30	TAMILSELVI	33415	58	4532/13	3796	Lt MRM	T3N1M0	6*4*3
31	KALAIARASI	35167	62	4632/13	3981	Rt MRM	T3N0M0	6*5*4
32	SELVI	37182	70	4976/13	4321	Lt MRM	T4bN1M0	5*4*3
33	MAHAMAYI	39876	64	5321/13	4543	Lt MRM	T3N1M0	6*5*3
34	JHANSI	41121	57	5543/13	4873	Rt MRM	T2N1M0	3*3*2
35	VANI	42311	48	5764/13	4976	Lt MRM	T2N1M0	3*3*2
36	MAHIMAI	44321	51	5871/13	5141	Rt MRM	T2N0M0	4*3*2
37	SADHANA	46431	49	6016/13	5211	Lt MRM	T3N1M0	7*6*5
38	REVATHY	47811	42	6143/13	5321	Lt MRM	T2N0M0	4*3*3
39	VASUMATHI	48765	44	6321/13	5331	Lt MRM	T3N0M0	5*4*3
40	VAIDHEGI	49012	49	6487/13	5432	Rt MRM	T1N0M0	2*2*1
41	REKHA	49812	29	6496/13	5561	Rt MRM	T1N0M0	2*2*1
42	KUMARI	50121	35	6675/13	5613	Lt MRM	T2N0M0	4*3*2
43	NALINI	51212	39	6875/13	5813	Rt MRM	T3N1M0	6*5*3
44	MEGALA	52312	47	6945/13	5913	Lt MRM	T2N1M0	4*3*2
44	MANIAMMA	53124	46	7076/13	6134	Rt MRM	T3N1M0	6*5*4
45	KUPPAMAL	54121	53	7132/13	6321	Rt MRM	T4bN1M0	5*4*3
46	NALINI	55132	55	7564/13	6453	Rt MRM	T2N0M0	4*3*2
47	PAPPATHY	56432	29	7613/13	6543	Lt MRM	T2N0M0	3*2*1
48	PARIMALAM	57543	38	7765/13	6654	Rt MRM	T3N0M0	6*4*3
49	SAROJA	58431	45	7865/13	6754	Lt MRM	T2N1M0	6*5*3
50	BEGUM	59546	49	7998/13	6854	Rt MRM	T1N0M0	2*2*1

SL. NO.	NAME	AGE	TYPE	HISTOLOGICAL GRADE	NODAL STATUS	RESECTED MARGINS	ER STATUS	PR STATUS	HER-2/neu	STAGE	TUMOUR SIZE(cm)
1	CHINNAMMAL	75	IDC-NOS	II	+	-	+	+	+	T4bN0M0	12*10*3
2	RAMZAN BEE	53	IDC-NOS	II	-	-	+	+	-	T2N0M0	3*3*2
3	CHANDRA	46	IDC-NOS	II	+	-	+	+	+	T2N0M0	2.5* 2* 2
4	VICTORIA	50	IDC-NOS	II	+	-	+	-	+	T4bN0M0	8*5*4
5	KALAISELVI	56	IDC-NOS	II	-	-	+	+	-	T3N0M0	6*4*2
6	KUMARI	76	MUCINOUS		-	-	+	+	-	T1NOMO	2*2*1
7	OMANA	61	IDC-NOS	I	-	-	-	+	-	T1N0M0	2*2*1
8	KAMATCHI	56	IDC-NOS	II		NA	-	+	+	T4BN0M0	6*5*3
9	SHAMIRA	40	IDC-NOS	II		NA	+	+	+	T4BN0M0	7*5*3
10	VIJALAKSHMI	26	IDC-NOS	II		NA	+	+	-	T3N1M0	6*5*3
11	KALA	35	IDC-NOS	II	-	-	-	+	-	T3 N0M0	6*4*3
12	LALITHA	50	IDC-NOS	III	+	-	+	+	+	T2N1M0	3*2*2
13	RAVANAMMA	41	ILC		+	NA	+	+	-	T3N1M0	6*5*4
14	NAGAMMAL	55	IDC-NOS	II	-	-	-	+	-	T1N0M0	2*2*1
15	SAKKAMMA	60	IDC-NOS	II	-	-	+	+	-	T2N0M0	3*3*2
16	YASODHA	54	IDC-NOS	II	-	-	+	+	-	T2N0M0	4*3*2
17	VIJAYA	35	IDC-NOS	II	+	-	-	-	+	T3N0M0	6*5*3
18	KANAGA	45	IDC-NOS	II	-	-	-	+	-	T2N0M0	4*3*3
19	RADHA	60	IDC-NOS	II	+	+	-	+	+	T4bN1M0	5*4*3
20	GNANASELVAM	56	IDC-NOS	I	+	-	+	+	-	T3N1M0	5*4*4
21	PREMA	53	IDC-NOS	II	+	-	+	+	-	T2N1M0	4*3*2
22	FATHIMA	48	IDC-NOS	III	+	-	+	+	+	T3N1M0	6*5*4
23	MOHANA	35	IDC-NOS	II	+	-	-	-	+	T4bN1M0	7*4*3

24	PARIMALA	53	IDC-NOS	II	+	-	+	+	-	T3N1M0	6*5*4
25	KAVYA	39	IDC-NOS	II	-	-	-	-	+	T1N0M0	2*2*2
26	MALATHY	44	IDC-NOS	III	-	-	-	-	+	T3N1M0	7*5*4
27	BANU	51	IDC-NOS	II	-	-	+	+	-	T3N0M0	6*5*3
28	LAVANYA	44	IDC-NOS	I	-	-	+	+	+	T2N0M0	4*4*3
29	MARIAMMAL	43	IDC-NOS	II	+	-	+	+	-	T4bN1M0	7*6*4
30	TAMILSELVI	58	IDC-NOS	II	-	-	+	+	+	T3N1M0	6*4*3
31	KALAIARASI	62	IDC-NOS	II	-	-	+	-	-	T3N0M0	6*5*4
32	SELVI	70	IDC-NOS	III	+	+	-	-	+	T4bN1M0	5*4*3
33	MAHAMAYI	64	IDC-NOS	II	-	-	+	+	+	T3N1M0	6*5*3
34	JHANSI	57	IDC-NOS	II	-	-	+	+	+	T2N1M0	3*3*2
35	VANI	48	IDC-NOS	II	-	-	+	+	-	T2N1M0	3*3*2
36	MAHIMAI	51	IDC-NOS	I	-	-	+	+	-	T2N0M0	4*3*2
37	SADHANA	49	IDC-NOS	III	+	-	-	-	+	T3N1M0	7*6*5
38	REVATHY	42	IDC-NOS	I	-	-	+	+	-	T2N0M0	4*3*3
39	VASUMATHI	44	IDC-NOS	II	-	-	+	+	-	T3N0M0	5*4*3
40	VAIDHEGI	49	ILC		-	-	-	-	-	T1N0M0	2*2*1
41	REKHA	29	IDC-NOS	I	-	-	+	+	-	T1N0M0	2*2*1
42	KUMARI	35	IDC-NOS	II	-	-	+	-	-	T2N0M0	4*3*2
43	NALINI	39	IDC-NOS	II	+	-	-	+	-	T3N1M0	6*5*3
44	MEGALA	47	IDC-NOS	II	-	-	-	+	-	T2N1M0	4*3*2
44	MANIAMMA	46	IDC-NOS	II	-	-	+	+	-	T3N1M0	6*5*4
45	KUPPAMAL	53	IDC-NOS	III	+	-	-	-	+	T4bN1M0	5*4*3
46	NALINI	55	IDC-NOS	I	-	-	+	+	-	T2N0M0	4*3*2
47	PAPPATHY	29	IDC-NOS	II	-	-	+	-	+	T2N0M0	3*2*1
48	PARIMALAM	38	IDC-NOS	II	-	-	+	+	-	T3N0M0	6*4*3
49	SAROJA	45	IDC-NOS	II	-	-	-	+	-	T2N1M0	6*5*3
50	BEGUM	49	IDC-NOS	I	-	-	+	+	-	T1N0M0	2*2*1

மார்பக புற்றுநோயில் ஹோர்மோன் ஏற்பிநிலையும் அதன் தொடர்பாக உயிர் தசைகூறுகள் தரபடுத்தல் பற்றியும், வயது மற்றும் நிணநீர்கணு ஈடுபாடு பற்றிய ஆய்வு

ஆய்வாளர் :டாக்டர் . இராணி சுகன்யா. இரா
முதுநிலை மேற்படிப்பு மாணவர்
அறுவை சிகிச்சை பட்டபடிப்பு

வழிகாட்டி :டாக்டர் .பேராசிரியர் டார்வின்
அறுவைசிகிச்சை பேராசிரியர்
அரசு ஸ்டான்லி மருத்துவமனை

பங்கேற்பாளரின் தகவல் படிவம்

நீங்கள் இந்த ஆய்வில் பங்கேற்க அழைக்க படுகிறிர்கள்.

இந்த ஆய்வில் பங்கேற்கும்முன்னர் இதன் நோக்கத்தையும் முறைகளையும் இதனால் ஏற்படகூடிய பின்விளைவுகளையும் ஏதேனையும் நீங்கள் அறிந்து கொள்ள ஆய்வாளர் அளிக்கும் தகவல் பின்வருமாறு.

மார்பகபுற்று நோயினால் பாதிகப்பட்ட நோயாளிகள் மட்டுமே இந்த ஆய்வில் எடுத்துக் கொள்ளபடுவீர்கள். உங்கள் நோயின் முழுவரலாறும், உங்களின் முழு உடல் பரிசோதனையும் தெளிவாகவும் விரிவாகவும் பதிவு செய்யப்படும். இரத்த பரிசோதனை மற்றும் நுண்கதிரியல் பரிசோதனைகளின் முடிவுகள் ஏற்றவாறு பதியப்படும். பரிசோதனைக்கு முன்னும் பின்னும் மற்றும் பரிசோதனையின் பொழுதும் உங்களிடம் ஏற்படும் உடல் நிலை மாற்றங்கள் பதிவு செய்யப்படும்.

இந்த ஆய்வின் முடிவுகள் மருத்துவ காரணங்களுக்காகவும் மருத்துவ கல்விக்காகவும் பயன்படும். இந்த ஆய்வு பற்றிய சந்தேகங்களுக்கு உரிய முறையில் விளக்கம் அளிக்கப்படும். தங்களை பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும்.

இந்த ஆய்வில் இருந்து எப்போது வேண்டுமானாலும் தாங்கள் எவ்வித முன்னறிவிப்பின்றியும், விலகி கொள்ளலாம். இவ்வாய்வில் பங்கேற்குமாறு கேட்டுக் கொள்கிறேன்.

இப்படிக்கு

ஆய்வாளர் கையொப்பம் நோயாளியின் கையொப்பம்

இராணி சுகன்யா. இரா பெயர்

மார்பக புற்றுநோயில் ஹோர்மோன் ஏற்பிநிலையும் அதன் தொடர்பாக உயிர் தசைகூறுகள் தரபடுத்தல் பற்றியும், வயது மற்றும் நிணநீர்கணு ஈடுபாடு பற்றிய ஆய்வு

ஆய்வாளர் :டாக்டர் . இராணி சுகன்யா. இரா
முதுநிலை மேற்படிப்பு மாணவர்
அறுவைசிகிச்சை பட்டபடிப்பு

வழிகாட்டி :டாக்டர் .பேராசிரியர் டார்வின்
அறுவைசிகிச்சை பேராசிரியர்
அரசு ஸ்டான்லி மருத்துவமனை

சுய ஒப்புதல் படிவம்

இந்த மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இவ்வாய்வில் தன்னிச்சையாகத் தான் பங்கேற்கிறேன் எந்த காரணத்தினாலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் விலகிக் கொள்ளலாம் என்று அறிந்துக் கொண்டேன்.

நான் ஆய்விலிருந்து விலகிக் கொண்டாலும் ஆய்வாளர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கோ அல்லது உபயோகிக்கவோ என் அனுமதி தேவையில்லை என அறிந்துக் கொள்கிறேன். என்னை பற்றிய தகவல்கள் இரகசியமாக பாதுகாக்கப்படும் என்பதை அறிவேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் ஆய்வாளர் அவர் விருப்பத்திற்கேற்ப எவ்விதமாக பயன்படுத்திக் கொள்ளவும் அதனை பிரசுரிக்கவும் என் முழுமனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்குக் கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரையின்படி நடந்துக் கொள்வதுடன் ஆய்வாளருக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை தெரிவிப்பேன் என உறுதிகூறுகிறேன். இந்த ஆய்வில் எனக்கு அனைத்து பரிசோதனைகளையும் சிகிச்சைகளையும் மேற்கொள்ள நான் முழுமனதுடன் சம்மதிக்கிறேன்.

இப்படிக்கு

ஆய்வாளர் கையொப்பம் நோயாளியின் கையொப்பம்

இராணி சுகன்யா. இரா பெயர்